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

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 10, 2020

Keros Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**001-39264**	**81-1173868**
(state or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

99 Hayden Avenue, Suite 120, Building E **Lexington, Massachusetts**	**02421**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 314-6297

Not applicable

(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**KROS**	**The Nasdaq Stock Market LLC**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

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. ☐

Item 8.01 Other Events.

Keros Therapeutics, Inc. (the "Company") is filing certain information for the purpose of updating the description of the Company's business contained in its other filings with the Securities and Exchange Commission. A copy of this additional disclosure is attached as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Company disclosure.

Forward-Looking Statements

This Current Report on Form 8-K, including Exhibit 99.1, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Current Report on Form 8-K, including Exhibit 99.1, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain. Forward-looking statements include, but are not limited to statements about:

- the timing of announcement of data for our Phase 2 clinical trial for our lead protein therapeutic product candidate, KER-050, in patients with myelodysplastic syndromes;
- the timing of initiation of our Phase 2 clinical trial for KER-050 in patients with myelofibrosis-associated cytopenias;
- the timing of announcement of data from our expanded Phase 1 clinical trial for our lead small molecule product candidate, KER-047, and the timing of initiation for future clinical trials for KER-047, including the timing of initiation of our three Phase 2 clinical trials of KER-047;
- the timing of initiation of our Phase 1 clinical trial for our third product candidate, KER-012;
- risks associated with the COVID-19 pandemic, which may adversely impact our business, preclinical studies and clinical trials;
- our ability to receive the required regulatory approvals and clearances to successfully market and sell our products in the United States and certain other countries;
- our ability to successfully advance our pipeline of additional product candidates;
- our ability to develop sales and marketing capabilities;
- the rate and degree of market acceptance of any products we are able to commercialize;
- the effects of increased competition as well as innovations by new and existing competitors in our market;
- our ability to obtain funding for our operations;
- our ability to establish and maintain collaborations;
- our ability to effectively manage our anticipated growth;
- our ability to maintain, protect and enhance our intellectual property rights and proprietary technologies;
- our ability to operate our business without infringing the intellectual property rights and proprietary technology of third parties;
- costs associated with defending intellectual property infringement, product liability and other claims;
- regulatory developments in the United States, Australia, New Zealand and other foreign countries;
- our ability to attract and retain qualified employees;
- our expectations regarding the period during which we qualify as an emerging growth company under the Jumpstart Our Business Startups Act of 2012;

- statements regarding future revenue, hiring plans, expenses, capital expenditures, capital requirements and stock performance; and
- the future trading prices of our common stock and the impact of securities analysts' reports on these prices.

In some cases, you can identify forward-looking statements by the words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "objective," "ongoing," "plan," "predict," "project," "potential," "should," "will," or "would," or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

You should read the section titled "Risk Factors" set forth in our Quarterly Report on Form 10-Q, filed with the SEC on August 13, 2020, and its other documents subsequently filed with or furnished to the SEC, for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. As a result of these factors, we cannot assure you that the forward-looking statements in this Current Report on Form 8-K, including Exhibit 99.1, will prove to be accurate. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. You should read this Current Report on Form 8-K, including Exhibit 99.1, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

KEROS THERAPEUTICS, INC.

By: /s/ Jasbir Seehra

Jasbir Seehra, Ph.D.
Chief Executive Officer

Dated: November 10, 2020

BUSINESS

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of novel treatments for patients suffering from hematological and musculoskeletal disorders with high unmet medical need. We are a leader in understanding the role of the Transforming Growth Factor-Beta, or TGF-ß, family of proteins, which are master regulators of red blood cell and platelet production as well as of the growth, repair and maintenance of muscle and bone. We have leveraged this understanding and developed a discovery approach to generate large and small molecules to address diseases of these tissues. Targeting TGF-ß signaling pathways has been clinically proven to elicit robust changes in blood cells, muscle and bone, which we believe provides a precedent and strong rationale for our strategy. Our lead protein therapeutic product candidate, KER-050, is being developed for the treatment of low blood cell counts, or cytopenias, including anemia and thrombocytopenia, in patients with myelodysplastic syndromes, or MDS, and in patients with myelofibrosis. We have initiated a Phase 2 clinical trial in patients with MDS and expect to report initial data from Part 1 of this trial in mid-2021. We also plan to initiate a Phase 2 clinical trial in patients with myelofibrosis in 2021. Our lead small molecule product candidate, KER-047, is being developed for the treatment of anemia resulting from iron imbalance, as well as for the treatment of fibrodysplasia ossificans progressiva, or FOP, a rare musculoskeletal disorder. We have completed our expanded Phase 1 clinical trial of KER-047 and expect to report topline data from this trial at a scientific conference by the end of 2020. Our third product candidate, KER-012, is being developed for the treatment of disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta, and for the treatment of pulmonary arterial hypertension, or PAH. We plan to progress KER-012 into a Phase 1 clinical trial in the second half of 2021. We believe KER-047 and KER-12 offer substantial opportunities for us to continue to apply our understanding of TGF-ß signaling pathways and expand our development programs in related hematological and musculoskeletal disorders with high unmet medical need.

KER-050 is an engineered ligand trap comprised of a modified ligand-binding domain of the TGF-ß receptor known as activin receptor type IIA, or ActRIIA, that is fused to the portion of the human antibody known as the Fc domain. KER-050 is designed to increase red blood cell and platelet production by inhibiting the signaling of a subset of the TGF-ß family of proteins to promote hematopoiesis. We believe KER-050 has the potential to provide benefit to patients suffering from red blood cell and platelet differentiation and maturation defects occurring across the spectrum from early through terminal stages of hematopoiesis, and consequently may be effective for many patients that have limited treatment options or are refractory to available therapies. We have completed a Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of KER-050 in healthy post-menopausal women. In this trial, we observed rapid and sustained increases in red blood cells, hemoglobin and reticulocytes, in addition to clinically meaningful increases in platelets after a single dose. Based on these findings and the results from preclinical studies, we believe KER-050 has a differentiated pharmacologic effect on red blood cells and platelets and has the potential to treat multiple cytopenias in diseases of ineffective hematopoiesis. In October 2020, we announced the dosing of the first two participants in our Phase 2 clinical trial evaluating KER-050 for the treatment of anemia and thrombocytopenia in very low-, low-, or intermediate-risk MDS. We expect to report initial data from Part 1 of this trial in mid-2021. Additionally, we plan to commence a Phase 2 clinical trial evaluating KER-050 for the treatment of patients with myelofibrosis-associated cytopenias in 2021.

KER-047 is designed to selectively and potently inhibit activin receptor-like kinase-2, or ALK2, a TGF-ß receptor. We believe that KER-047 has the potential to ameliorate excessive ALK2 signaling, which is directly implicated in anemias arising from iron imbalance and musculoskeletal disorders where the transformation of soft tissue into bone, referred to as heterotopic ossification, leads to devastating immobility. We are developing KER-047 for the treatment of anemia resulting from iron imbalance as a direct consequence of elevated ALK2 signaling, including our initial target, iron-refractory iron deficiency anemia, or IRIDA. We are also developing KER-047 as a treatment for FOP, a rare genetic disease resulting from mutations in the ALK2 receptor that results in gain-of-function activity. In these patients, soft tissue, including muscles and tendons, develops normally, but remodels into bone after injury. In August 2020, we announced the completion of our planned single and multiple ascending dose cohorts in a Phase 1 clinical trial of KER-047 in healthy volunteers, as well as the expansion of this trial to evaluate additional cohorts of healthy volunteers. We reported topline data from the planned cohorts of this trial in August 2020. In these cohorts, we observed dose-dependent

increases in serum iron. We also observed increases in reticulocyte hemoglobin, which is a measure of hemoglobin content from newly-produced immature red blood cells, in the volunteers who received KER-047. One additional cohort of healthy volunteers was evaluated in the trial expansion. Data from this cohort support the effect of KER-047 observed in the planned cohorts. We terminated the trial after determining that the data from this cohort, in addition to the data from the planned cohorts of the trial, were sufficient to inform the design of the expected Phase 2 clinical trials of KER-047, and expect to report topline data from this trial at a scientific conference by the end of 2020. As the data from this additional cohort were deemed sufficient to provide the necessary information, we currently do not plan to expand this trial into any additional cohorts of healthy volunteers. We expect to commence two Phase 2 clinical trials, one in patients with iron deficiency anemia, or IDA, and one in patients with IRIDA, in 2021.

KER-012 is designed to bind to and inhibit the signaling of TGF-ß ligands, including activin A and activin B, which are key regulators of bone remodeling that act to suppress bone growth, to potentially increase bone mass. We believe that KER-012 has the potential to increase the signaling of bone morphogenic protein, or BMP, pathways through this inhibition of activin A and activin B signaling, and consequently treat diseases such as PAH that are associated with reduced BMP signaling due to inactivating mutations in the BMP receptors. We are developing KER-012 for the treatment of disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta, and for the treatment of PAH. In a rat model of PAH, rats receiving a rodent version of KER-012, or RKER-012, were protected from the thickening of the right ventricular wall. In addition, rats receiving a rodent version of KER-012 were protected from PAH-associated bone loss which we believe demonstrates proof-of-mechanism of KER-012 for the treatment of PAH and bone loss. We plan to advance KER-012 into a Phase 1 clinical trial in the second half of 2021.

Our strategy focuses on the role of members of the TGF-ß family of proteins in the development of blood cells, muscle and bone. Aged and damaged cells are routinely replaced by new cells in normally functioning organs. These new cells are derived from stem cells that have the ability to differentiate into cells with specialized function when appropriate signals are provided to maintain the homeostatic state of the tissue. Members of the TGF-ß family of proteins, including activins and bone morphogenetic proteins, or BMPs, provide the necessary signals for this process of self-renewal and repair.

We seek to address the limitations of current therapeutic approaches to treating diseases whose manifestations are linked to dysfunction of TGF-ß signaling pathways by:

- Leveraging our comprehensive insights into the TGF-ß signaling pathways to discover therapeutics to treat hematological and musculoskeletal disorders.
- Expanding our library of proprietary molecules that are engineered to induce desired biological effects, such as increased blood cell production, inhibit heterotopic ossification and increased muscle and bone mass.
- Engineering proprietary molecules to selectively target specific proteins in the TGF-ß signaling pathways to provide therapeutic benefit while potentially minimizing safety risks.
- Developing product candidates for the treatment of diseases where targeting the TGF-ß signaling pathways has clinical validation or biological rationale to improve our probability of success in the clinic.
- Targeting the TGF-ß family of proteins, which are highly conserved throughout evolution, permitting the use of animal models to potentially predict with high confidence the therapeutic benefit in patients.

We are led by a highly experienced management team and scientific advisory board who have more than 100 combined years of research and development on therapeutics in the TGF-ß family of proteins. Our team has collectively worked on marketed therapeutics such as Reblozyl, Tecfidera, Kalydeco and Waylivra, and led drug discovery and clinical development at companies including Acceleron Pharma Inc., Biogen Inc., Wyeth Pharmaceuticals Inc., Seres Therapeutics, Inc., Vertex Pharmaceuticals Incorporated and Akcea Therapeutics, Inc.

Our Pipeline

The following table sets forth our product candidates, their current development stages and anticipated upcoming milestones.

Program	Asset	Phase of Development				Status	Next Milestones*
		Preclinical	Phase 1	Phase 2	Phase 3		
Hematology	KER-050 (therapeutic protein)	Myelodysplastic syndromes (MDS)				Initiated Phase 2 clinical trial	Initial data: mid-2021
		Myelofibrosis (MF)				Completed Phase 1 clinical trial	Initiate Phase 2 clinical trial: 2021
Hematology / Musculoskeletal	KER-047 (small molecule)	Iron deficiency anemia				Completed expanded Phase 1 clinical trial	Present topline data: end of 2020
		Anemia from high hepcidin					
		Fibrodysplasia Ossificans Progressiva (FOP)					
Preclinical Pipeline	KER-012 (therapeutic protein)	Pulmonary arterial hypertension				Ongoing preclinical studies	Initiate Phase 1 clinical trial: H2 2021
		Bone disorders					

* Anticipated clinical milestones are subject to the impact of COVID-19 on our business.

Our Strategy

Our mission is to deliver significant clinical benefit to patients suffering from hematological and musculoskeletal diseases by developing differentiated product candidates that are designed to alter TGF-ß signaling pathways. The key elements of our strategy include:

- *Rapidly advance the clinical development of KER-050 for the treatment of patients with MDS- and myelofibrosis-associated cytopenias.* We have generated preliminary data in our Phase 1 clinical trial of KER-050 in healthy post-menopausal women and have initiated a Phase 2 clinical trial evaluating KER-050 for the treatment of anemia and thrombocytopenia in participants with very low-, low-, or intermediate-risk MDS who either have or have not previously received treatment with an erythropoiesis-stimulating agent. We also plan to commence a Phase 2 clinical trial evaluating the treatment of patients with myelofibrosis-associated cytopenias in 2021.
- *Rapidly advance the clinical development of KER-047 for the treatment of anemias resulting from iron imbalance and musculoskeletal disorders where heterotopic ossification leads to devastating immobility.* We have generated preliminary topline data in a Phase 1 clinical trial of KER-047 in healthy volunteers, and expanded this trial to evaluate additional cohorts of healthy volunteers. One additional cohort of healthy volunteers was evaluated in the trial expansion. We terminated the trial after determining that the data from this cohort, in addition to the data from the planned cohorts, were sufficient to inform the design of the expected Phase 2 clinical trials of KER-047, and expect to report topline data from this trial at a scientific conference by the end of 2020. We also expect to commence two Phase 2 clinical trials, one in patients with IDA and one in patients with IRIDA, in 2021. Following the completion of the expected Phase 2 clinical trial in patients with IDA, we plan to commence a Phase 2 clinical trial in patients with FOP. We also intend to develop KER-047 as a potential treatment option for patients who manifest anemia caused by iron imbalance as a secondary consequence of more common diseases.
- *Advance KER-012 into and through clinical development for the treatment of disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta, and for the treatment of PAH.* We have generated preclinical data that we believe demonstrated proof-of-mechanism of KER-012 for the treatment of disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta, and for the treatment of PAH. We plan to advance KER-012 into a Phase 1 clinical trial in the second half of 2021.

- *Pursue development and, if approved, commercialization of our product candidates in indications and regions where we believe we can maximize their value independently or through strategic collaborations.* We plan to independently advance our product candidates in indications and regions that we believe have clearly defined regulatory paths and commercialization strategies. We intend to opportunistically evaluate strategic collaborations to maximize the potential commercial value of our product candidates and discovery programs.
- *Leverage our proprietary discovery approach and knowledge base to develop new therapeutics.* Our discovery efforts are focused on expanding our pipeline of wholly-owned assets for the treatment of hematological and musculoskeletal diseases. Accordingly, we intend to identify and develop product candidates to treat diseases where targeting the TGF-ß signaling pathways has clinical validation or biological rationale.

Our Hematology Program

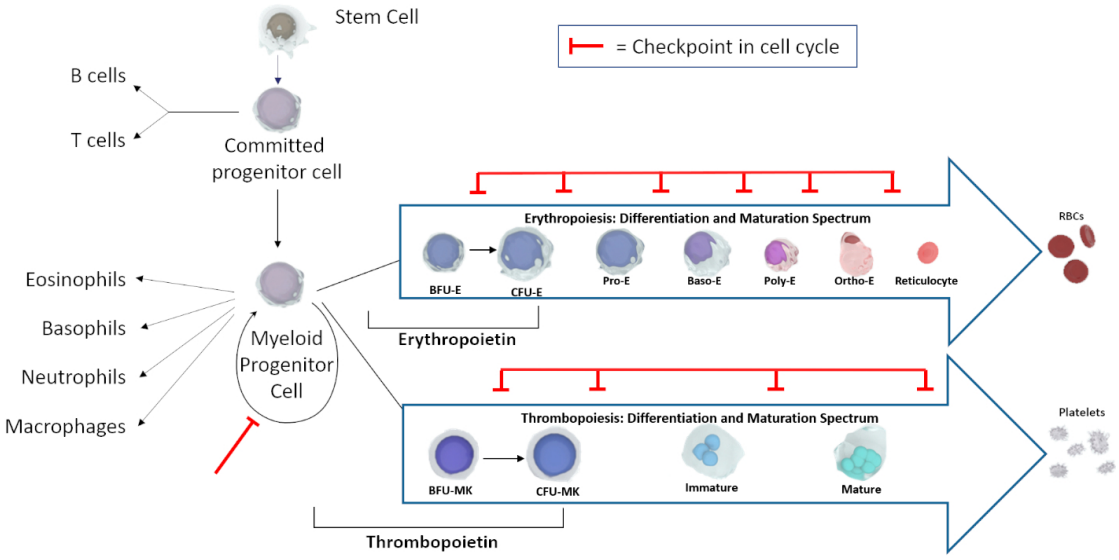
Our two lead product candidates, KER-050 and KER-047, are designed to target TGF-ß signaling pathways to address diseases that arise from ineffective hematopoiesis as well as anemias that result from iron imbalance.

Hematopoiesis

The primary cellular components of blood are red blood cells, white blood cells and platelets. The function of red blood cells is to distribute oxygen to tissues throughout the body and to carry waste carbon dioxide back to the lungs. White blood cells are responsible for the immune response through coordinated surveillance and targeting of pathogens, infected or aberrant cells and cell debris. Platelets are a key component of the coagulation system and are responsible for stopping bleeding by forming a blood clot.

Hematopoiesis is the production of red blood cells, white blood cells and platelets from common progenitor stem cells, or progenitor cells. This process begins when a hematopoietic progenitor cell becomes committed to a specific cellular lineage. These cells progress through a series of intermediate stages before becoming a mature cell with a specialized function. At any given time, pools of each progenitor cell are maintained and primed to rapidly respond to a reduction of red blood cells, white blood cells and platelets. The graphic below depicts the stages of hematopoiesis for red blood cells and platelets.

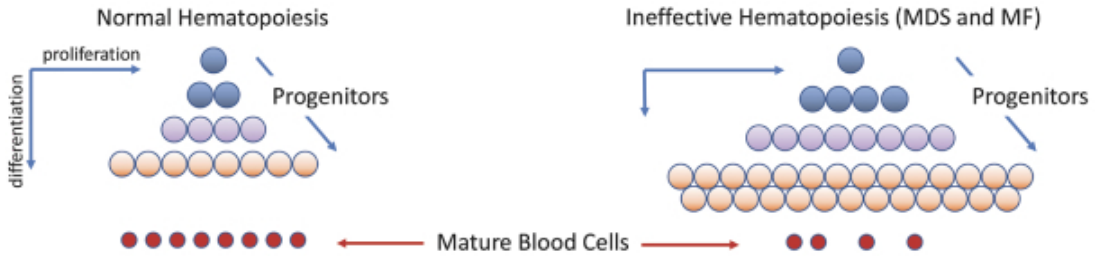
Stages of Hematopoiesis



TGF-ß signaling pathways involving activins prevent differentiation in order to maintain progenitor cells in a quiescent state while others involving BMPs promote differentiation of progenitor cells. Homeostasis of this process is essential to ensure all cell types are properly replenished in the blood.

In many hematological disorders, there is abnormal proliferation and differentiation of the progenitor cells for red blood cells, platelets and neutrophils. This failure to produce fully mature cells is termed ineffective hematopoiesis, and may be due to single or multiple defects that can lead to a hyperproliferation or a shortage of progenitor cells.

These changes have clinical consequences: a lack of red blood cells leads to anemia, a lack of platelets hampers clotting, resulting in increased incidence of bleeding events, and a lack of neutrophils increases susceptibility to infection. The failure of progenitor cells to differentiate can also lead to a build-up of these cells, resulting in bone marrow failure and fibrotic disease. The graphic below provides an illustration of the difference in the number of progenitor cells and mature bloods cells that are produced in normal hematopoiesis and in ineffective hematopoiesis.



Another critical component in red blood cell development is the production of hemoglobin, an iron-containing protein that delivers oxygen to cells and removes carbon dioxide. The synthesis of hemoglobin requires that sufficient levels of iron are present in the bone marrow and if iron levels are too low, it can result in a failure to produce sufficient numbers of red blood cells. Anemia is a common consequence of diseases where normal iron mobilization is hindered.

KER-050: For the Treatment of Ineffective Hematopoiesis to Address Cytopenias

We are developing KER-050, our lead protein therapeutic product candidate, for the treatment of cytopenias that occur due to ineffective hematopoiesis, including anemia and thrombocytopenia, in patients with MDS and in patients with myelofibrosis. KER-050 is designed to benefit patients suffering from defects in red blood cell and platelet differentiation and maturation across the spectrum from early through terminal stages of hematopoiesis. Consequently, KER-050 may be effective for many patients that have limited treatment options or are refractory to available therapies.

Myelodysplastic Syndromes

Myelodysplastic syndromes, or MDS, is a collection of bone marrow disorders characterized by ineffective hematopoiesis, often with a dramatic expansion of progenitor cells that are unable to mature into functioning blood cells. In the United States, there are 60,000 to 170,000 patients with MDS and 15,000 to 20,000 new cases of MDS reported each year. MDS predominantly affects older adults, with approximately 75% of patients aged 60 years or older at diagnosis. Median survival ranges from approximately nine years for very low-risk patients to less than a year for high-risk patients.

Cytopenias in MDS are caused by defects occurring across the various stages of hematopoiesis, from the self-renewal of progenitor cells to differentiation in early through terminal stages. Anemia is the most frequent consequence of ineffective hematopoiesis in patients with MDS due to low red blood cell production, and impacts 90% of MDS patients, with approximately 40% becoming transfusion dependent. Another consequence is thrombocytopenia, a deficiency of platelets in the blood, which is impaired blood clotting that can cause bleeding. The prevalence of thrombocytopenia in patients with MDS has been reported at 40% to 65%. A deficiency of neutrophils in the blood, or neutropenia, also increases the risk of serious infections in patients with MDS and has been reported to affect approximately 20% of patients with MDS.

To guide decisions on risk stratification and the treatment of patients with MDS, clinicians typically use the International Prognostic Scoring System-Revised, or the IPSS-R. The IPSS-R incorporates information on bone marrow blast percentage, karyotype and presence and severity of cytopenias in order to classify patients with MDS into groups based on the risk of progression to acute myeloid leukemia, ranging from very low-risk to high-risk. Patients are further classified into high transfusion burden and low transfusion burden categories based on the number of units of transfused red blood cells they receive.

A second classification system is the World Health Organization, or WHO, system, which is based on a combination of morphology, immunophenotype, genetics and clinical features. The WHO classification system includes a subgroup of patients with MDS that show the presence of iron deposits around the mitochondria, known as ring sideroblasts. These patients are commonly referred to as RS positive and comprise approximately 15% of incident patients with MDS, and splicing factor mutations, such as *SF3B1*, are highly correlated with these patients. Patients with splicing factor mutations often have been observed to have defects in the differentiation of red blood cells at the terminal stage. The majority of patients with MDS that develop cytopenias lack ring sideroblasts or a single, defining splicing factor mutation and are termed non-RS. These non-RS patients have differentiation and maturation defects occurring across the spectrum from early through terminal stages of hematopoiesis.

Limitations of Current Treatment Options for Cytopenias in Patients with MDS

Patients with MDS-associated anemia are generally treated with red blood cell transfusions and erythroid stimulating agents, or ESAs, which are not approved for such treatment. The treatment of MDS-associated thrombocytopenia is platelet transfusions and platelet-stimulating agents.

Severe cytopenia and transfusion dependence are independent predictors of poor prognosis for patients with MDS and are inversely correlated with quality of life. Red blood cell and platelet transfusions provide temporary benefits to patients with MDS, but are associated with both acute and chronic health risks, including risk of bacterial infection and allergic reactions to the donor blood, and place a significant burden on both the patient and the healthcare system. Red blood cell transfusions are also associated with iron overload, which can lead to organ dysfunction over time. Additionally, the benefit from a platelet transfusion is typically short-lived and availability is limited. Platelet-stimulating agents for the treatment of thrombocytopenia, which are not currently indicated for MDS, carry the risk of thromboembolic events and bone marrow fibrosis.

ESAs are a class of drugs that work on the proliferation stage of red blood cell development by expanding the pool of early-stage progenitor cells. While ESAs have been shown to alleviate anemia in a subset of patients with MDS, patients that have elevated endogenous erythropoietin levels are unlikely to respond. In two controlled Phase 3 clinical trials evaluating darbepoetin alfa (Aranesp) for the treatment of MDS-associated anemia, 15% to 31% of patients responded. However, this response was limited to patients with mildly elevated endogenous erythropoietin levels and to patients who largely did not require regular red blood cell transfusions. These treatment options also represent a significant burden to patients, as they must be administered up to three times a week. Additionally, the effect of ESAs is limited to the red blood cell lineage and, therefore, ESAs only treat MDS-associated anemia and do not provide benefit to cytopenia of other cell lineages, including thrombocytopenia and neutropenia.

Reblozyl, a TGF-ß-based erythroid maturation agent, is designed to promote the terminal differentiation of red blood cells through inhibition of selected endogenous TGF-ß superfamily ligands. The characteristics of response were defined in a Phase 2 clinical trial of Reblozyl in patients with MDS. Consistent with the mechanism of Reblozyl on the terminal stages of erythropoiesis, the majority of responders were determined to have an *SF3B1* splicing factor mutation. Additionally, the responders were characterized as having increased erythroid progenitor cells in the bone marrow, while patients with fewer erythroid progenitor cells in the bone marrow did not achieve hematological improvement. We believe this indicates that Reblozyl is limited to its effect on terminal differentiation of erythropoiesis and does not affect the early stages of differentiation.

Reblozyl received approval from the U.S. Food and Drug Administration, or the FDA, in April 2020 for the treatment of anemia in adult RS positive patients with very low- to intermediate-risk MDS that failed an erythropoiesis stimulating agent and required two or more units of red blood cells over eight weeks. The approval was based on a single Phase 3 clinical trial of Reblozyl that was conducted in RS positive, very low- to intermediate-risk patients with MDS. This trial included both patients with low transfusion dependence requiring

fewer than four units of red blood cells over eight weeks and patients with high transfusion dependence requiring four or more units of red blood cells over eight weeks. In this trial, 37.9% of the RS positive patients treated with Reblozyl achieved the primary endpoint of transfusion independence, compared to 13.2% of patients that received placebo. The highest proportion of responders to Reblozyl were those with low transfusion dependence, while only a few high transfusion burden patients achieved transfusion independence despite being RS positive patients.

Accordingly, we believe that additional treatment options will be needed to address anemia in the heterogeneous non-ring sideroblast MDS population, to provide clinical benefit to the RS positive population regardless of transfusion burden and to address other cytopenias, such as thrombocytopenia.

KER-050 is designed to alter TGF-ß signaling pathways at multiple stages of hematopoietic differentiation in both red blood cells and platelets. Consequently, we believe KER-050 has the potential to provide therapeutic benefit in a broader subset of patients with MDS that have varying defects in commitment, differentiation and maturation of multiple cell types found in blood.

Myelofibrosis

Myelofibrosis is a group of rare cancers of the bone marrow in which the marrow is replaced by scar tissue and is not able to produce healthy blood cells. Myelofibrosis is characterized by ineffective hematopoiesis, an enlarged spleen, bone marrow fibrosis and shortened survival. Patients often experience multiple disease-associated and treatment-emergent cytopenias, including anemia and thrombocytopenia.

The ineffective hematopoiesis in myelofibrosis is driven by molecular abnormalities in the Janus kinase 2, or JAK2, -signal transducers and activators of transcription, or JAK-STAT, signaling pathway of transcriptional activators. Specifically, JAK2 activation leads to proliferation of red blood cell progenitors and platelet progenitors, or megakaryocytes, that fail to mature to platelets. Additionally, megakaryocyte dysplasia/hyperplasia has been implicated in inducing bone marrow fibrosis in patients with myelofibrosis. The inability of megakaryocytes to fully differentiate leads to the release of pro-inflammatory and pro-fibrotic factors that results in scarring of the bone marrow, which further exacerbates the myelofibrosis-associated cytopenias.

Myelofibrosis is a relatively rare condition with an identified prevalence of 16,000 to 18,500 patients in the United States. Approximately 3,000 new patients are diagnosed with myelofibrosis each year, and the median age at diagnosis is approximately 60 years. Currently, there are limited therapeutic options to address the myelofibrosis-associated cytopenias. Within a year of diagnosis, 38% of patients with myelofibrosis are red blood cell transfusion dependent and eventually nearly all will develop transfusion dependence. Additionally, within a year of diagnosis, 26% of patients with myelofibrosis will develop thrombocytopenia and 51% will develop anemia.

Limitations of Current Treatment Options for Cytopenias in Patients with Myelofibrosis

There are no approved pharmacological treatments for myelofibrosis-associated cytopenias. The National Comprehensive Cancer Network describes all therapeutic options to address myelofibrosis-associated cytopenias, including transfusions, as only minimally effective.

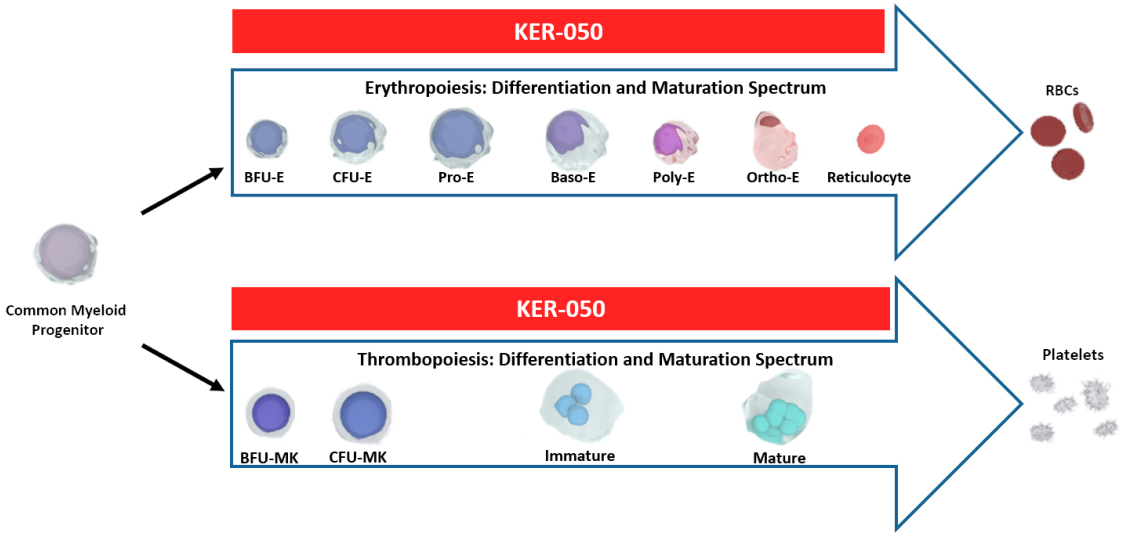
Currently approved products for the treatment of myelofibrosis, including JAK inhibitors ruxolitinib (Jakafi) and fedratinib (Inrebic), have been observed to exacerbate myelofibrosis-associated cytopenias. In a third-party Phase 3 clinical trial of Jakafi and a third-party Phase 3 clinical trial of Inrebic, treatment led to significant reductions in spleen volume and improvement in total symptom scores. However, JAK inhibitors interfere with normal hematopoiesis and treatment with Jakafi and Inrebic also resulted in clinically significant anemia and thrombocytopenia in these Phase 3 trials. Approximately 45% of patients in the Phase 3 clinical trial of Jakafi developed treatment-related grade 3 or 4 anemia. Grade 3 or higher adverse events of anemia and thrombocytopenia were observed in approximately 34% and 12%, respectively, of patients evaluated in the Phase 3 clinical trial of Inrebic. The treatment-related cytopenias led to severe complications, dose reductions and reduced compliance.

We believe KER-050 has the potential to ameliorate myelofibrosis-associated cytopenias.

Our Solution: KER-050

KER-050 is a ligand trap comprised of a modified ligand-binding domain of ActRIIA that is fused to the portion of the human antibody known as the Fc domain. KER-050 is designed to bind to and inhibit the signaling of TGF-ß ligands involved in the regulation of hematopoiesis, resulting in increased red blood cell and platelet production. Combined data from our preclinical studies and our Phase 1 clinical trial demonstrate that treatment with KER-050 increased red blood cell and platelet production. These data indicate that KER-050 is differentiated from available therapies because it appears to have both sustained and rapid effects on multiple cellular lineages in the hematopoietic pathway. We believe KER-050's promotion of differentiation of early- and terminal-stage progenitor cells contributes to these sustained and rapid effects, respectively, and consequently, KER-050 may be effective for many patients that are refractory to available therapies and may potentially provide benefit in multiple cytopenias simultaneously.

Mechanism of Action of KER-050



We intend to develop KER-050 for the treatment of both MDS- and myelofibrosis-associated cytopenias. We believe KER-050 has the potential to overcome limitations of current treatment options for MDS- and myelofibrosis-associated cytopenias. We believe the potential advantages of KER-050 compared to current treatment options include:

- *Dual mechanism affecting both the early and terminal stages of erythropoiesis.* Patients with MDS can have defects occurring anywhere along the differentiation and maturation spectrum of erythropoiesis, and often have multiple mutations that cause ineffective erythropoiesis. By acting on cell types throughout the erythropoiesis pathway, KER-050 may lead to robust responses in RS positive patients who have a characteristic defect in terminal maturation, and may also address anemia in the broader MDS population that has defects in earlier-stage erythroid cell development.
- *Increased platelet counts in blood.* Ineffective hematopoiesis in patients with MDS and in patients with myelofibrosis can result in thrombocytopenia, which can lead to an increased risk of bleeding events. We believe treatment with KER-050 has the potential to address the MDS- and myelofibrosis-associated thrombocytopenia.
- *Reduced accumulation of progenitor cells.* Ineffective hematopoiesis in patients with MDS and in patients with myelofibrosis can be caused by excessive production of blood cell progenitors that are unable to complete differentiation and ultimately become mature blood cells. We believe treatment with KER-050 will stimulate these progenitors to progress to maturation, ameliorating the accumulation of these cells that lead to MDS- and myelofibrosis-associated cytopenias.
- *Robust and sustained increase in red blood cells, hemoglobin and reticulocytes, supporting monthly or less frequent dosing.* ESAs can require dosing up to three times a week. We believe that treatment

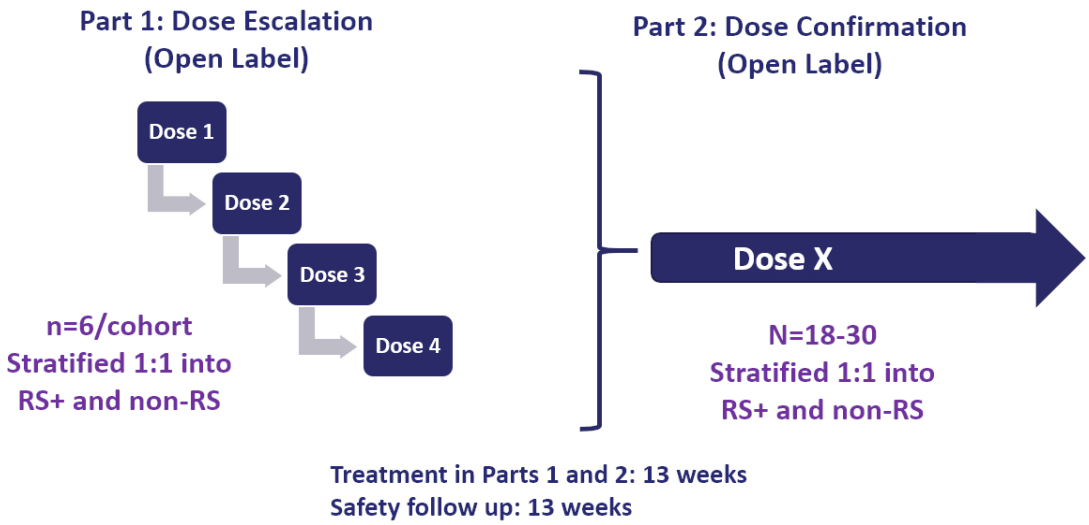
with KER-050 has the potential to reduce the frequency of dosing to every four weeks or less frequently, thereby decreasing the burden on patients and potentially improving compliance.

Ongoing Phase 2 Clinical Trial in Patients with Myelodysplastic Syndromes

We are conducting an open label, two-part, multiple ascending dose Phase 2 clinical trial to evaluate KER-050 in participants with very low-, low-, or intermediate-risk MDS who either have or have not previously received treatment with an ESA.

The primary objective of this trial is to assess the safety and tolerability of KER-050 in participants with MDS that either have ring sideroblasts (RS+) or do not have ring sideroblasts (non-RS). We expect to use the data from Part 1 of this trial to help define the dose level to be evaluated in Part 2 of this trial, in which the primary objective is confirmation of the safety and tolerability of the selected dose levels. The secondary objectives of this trial are to evaluate the pharmacokinetics, pharmacodynamics and efficacy of KER-050. The trial design is summarized in the figure below.

Phase 2 Clinical Trial Design



Clinical Development Strategy

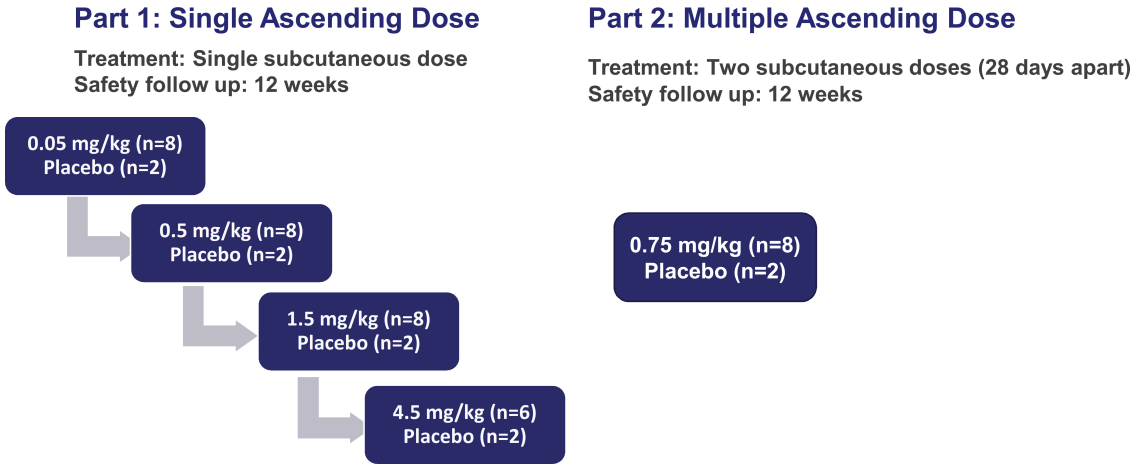
We expect to report initial data from Part 1 of the Phase 2 clinical trial in patients with MDS in mid-2021. We also expect to commence an open-label Phase 2 clinical trial evaluating the treatment of patients with myelofibrosis-associated cytopenias in 2021.

Completed Phase 1 Clinical Trial

In January 2020, we completed a randomized, double-blind, placebo-controlled, two-part, dose-escalation Phase 1 clinical trial of KER-050 in 48 healthy post-menopausal women. The primary objectives of this trial were safety, tolerability and pharmacokinetics. We also investigated changes in hematology and bone biomarkers in this clinical trial.

In Part 1 of this trial, 30 subjects received a single dose of KER-050 and eight subjects received a single dose of placebo, each administered subcutaneously with a 12-week safety follow-up. The subjects were enrolled in sequential single-ascending dose escalation cohorts of up to ten subjects each. In Part 2 of this trial, eight subjects received KER-050 and two received placebo, administered subcutaneously, on two occasions 28 days apart, with a 12-week safety follow-up after the second dose. In Part 2 of this trial, only one dose level was evaluated, as it was deemed to provide the necessary data, in addition to that from Part 1 of the trial, to inform the design of the Phase 2 clinical trials of KER-050 in patients with MDS and in patients with myelofibrosis.

The trial design is summarized in the figure below.



Observed tolerability data

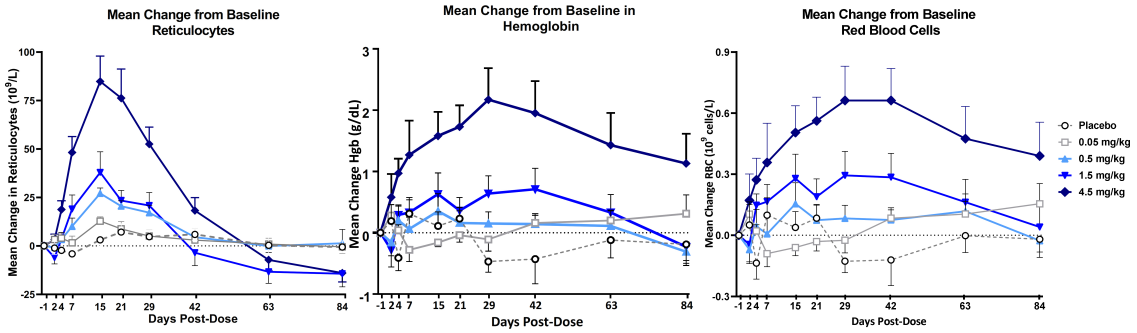
KER-050 was well tolerated in this Phase 1 clinical trial at dose levels up to 4.5 mg/kg, the highest dose level tested, and multiple doses of 0.75 mg/kg. While one subject in the placebo group withdrew consent, there were no discontinuations due to treatment-related adverse events. No treatment-related serious adverse events were reported. The most common adverse events observed in subjects in this trial were nausea, gastroenteritis, injection site erythema and, consistent with the mechanism of action of KER-050, increased hemoglobin and hypertension. The reversible, mild hypertension events were observed in subjects with an approximately 3 g/dL increase in hemoglobin.

Long half-life observed, potentially supporting monthly or less frequent dosing

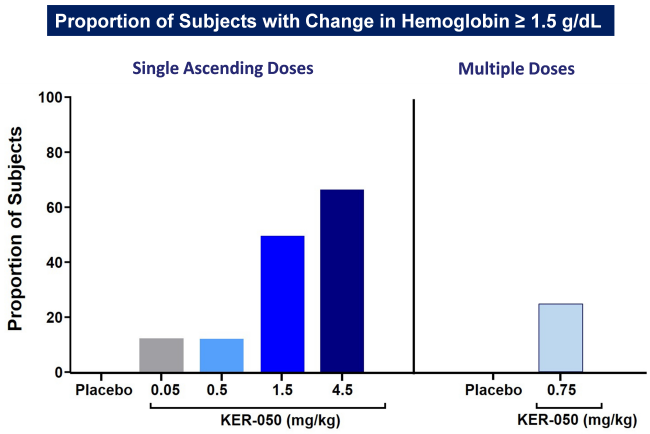
We observed that KER-050 drug levels were dose proportional in Part 1 of this trial, with a mean half-life of approximately ten to 12 days. The half-life coupled with the pharmacodynamic effect observed in the hematologic parameters support the potential for administration of monthly or less frequent dosing, which we believe will decrease the burden on patients and improve compliance.

Rapid and sustained increases in mean reticulocyte counts, hemoglobin, red blood cell counts and platelet counts observed

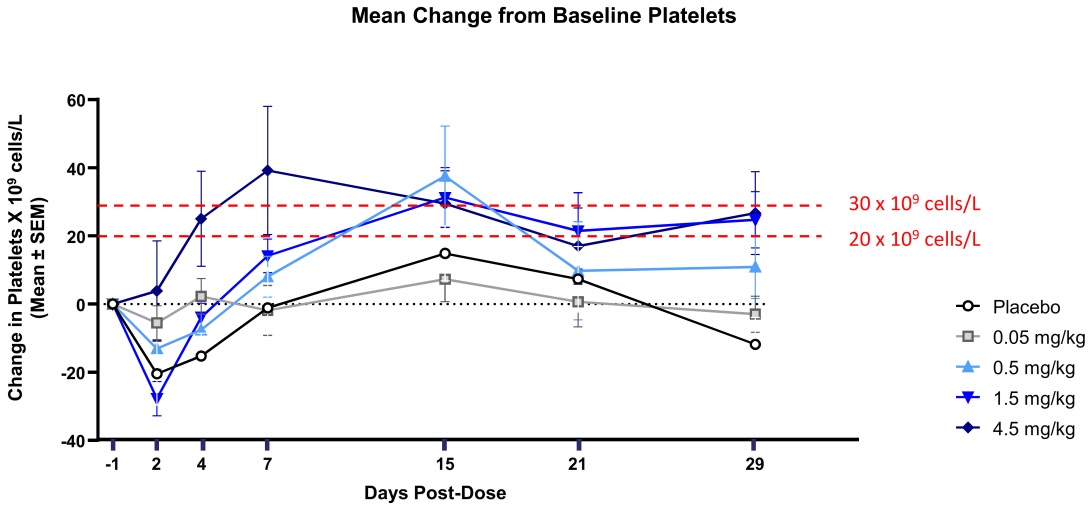
In Part 1 of this trial, we observed rapid and sustained increases in mean reticulocyte counts, hemoglobin, red blood cell counts and platelet counts. Consistent with the underlying biology, increases in reticulocytes were observed early with increases of hemoglobin following thereafter. Increases in reticulocytes were observed as early as Day 2 and reached a peak around Day 15. Increases in hemoglobin concentration were also observed as early as Day 2, reached a peak around Day 29 and remained elevated for several weeks.



We also observed a dose-dependent increase in the proportion of subjects with hemoglobin increases of at least 1.5 g/dL. We believe a 1.5 g/dL increase would be considered clinically meaningful in patients with low red blood cell counts.



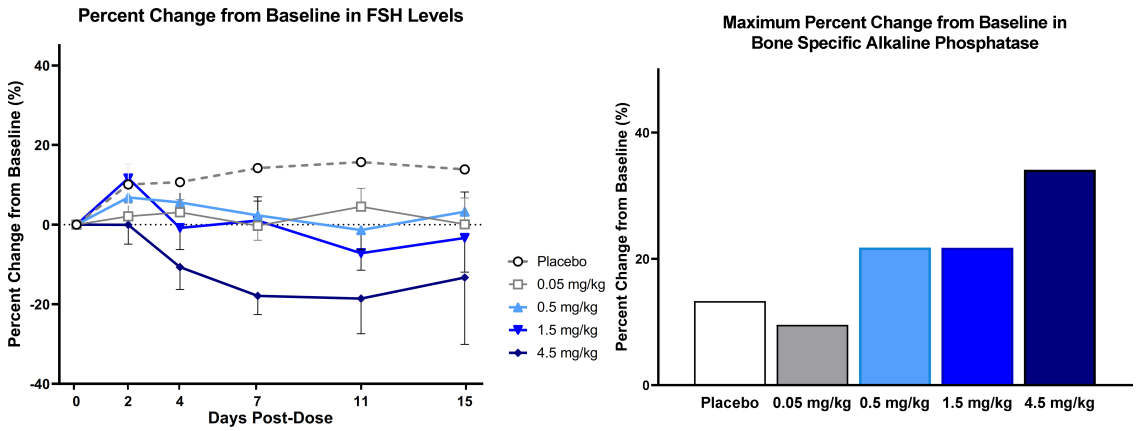
In addition to the changes in erythroid parameters, robust, dose-dependent increases in platelet count were observed after a single dose of KER-050. All subjects who received a 4.5 mg/kg dose of KER-050, the highest dose evaluated, demonstrated an increase of 30 x 10^9 cells/L or greater at any one point in the trial, which we believe would be considered clinically meaningful in patients with low platelet counts.



We believe the rapid onset and durability of increased hemoglobin and platelet count observed in our Phase 1 clinical trial supports the potential for a dual effect of KER-050 on both early-stage differentiation and terminal maturation.

Additionally, we observed reductions in follicle-stimulating hormone, a biomarker of activin inhibition, following administration of KER-050, which we believe is indicative of target engagement and activin inhibition. We also

observed an increase in bone-specific alkaline phosphatase, a biomarker of bone remodeling, which we believe demonstrates that KER-050 has the potential to increase bone mass.



Preclinical Data

KER-050 was observed to inhibit ligands that signal through activin receptors in *in vitro* assays, and to potently regulate hematopoiesis in *in vivo* studies. Specifically, KER-050 demonstrated in these studies:

- high affinity for and potent inhibition of ligands involved in the regulation of hematopoiesis;
- increased red blood cell production in mice and non-human primates; and
- increased maturation of early- and terminal-stage erythroid progenitors.

KER-050 observed to target ligands that signal through ActRIIA and ActRIIB

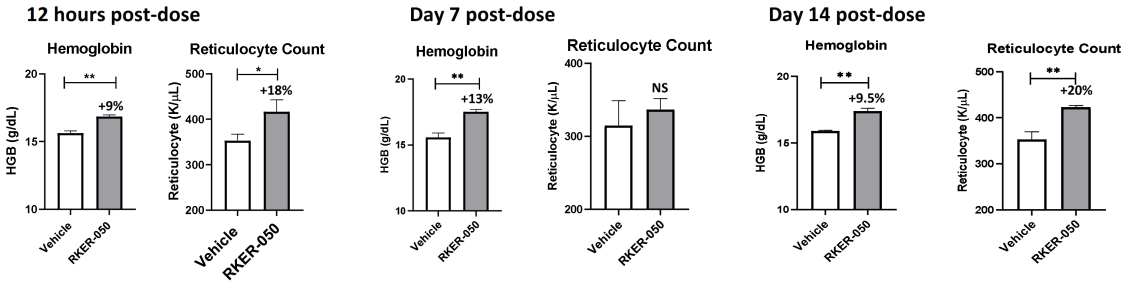
KER-050 is a modified ActRIIA ligand trap that contains sequences from both wild-type ActRIIA and wild-type activin receptor type IIB, or ActRIIB. KER-050 was observed to bind to and inhibit multiple ligands that signal through these cell surface receptors, including activin A, activin B and growth differentiation factor 11. These ligands are key regulators of hematopoiesis that restrict blood cell progenitors from continuing through differentiation and developing into mature cells with specialized function. The KER-050-mediated inhibition of these regulators stimulated the progenitors to progress to maturation and, consequently, increased the number of mature cells in the blood.

Mouse version of KER-050 observed to potently stimulate red blood cell parameters and to increase the populations of erythroid progenitors

In a preclinical study conducted in mice, a single, subcutaneous 10 mg/kg dose of a mouse version of KER-050, or RKER-050, increased red blood cell parameters, including red blood cell number and reticulocytes, as early as 12 hours and continuing to at least 14 days post-dose. We believe the rapid onset of the effect is consistent with terminal maturation of late-stage erythroid precursors. RKER-050 has been

modified to have a murine Fc domain in place of the human Fc domain present in KER-050, in order to minimize results confounded by the development of anti-drug antibodies in mice treated with a human protein.

Increase in Red Blood Cells and Reticulocytes in Mice

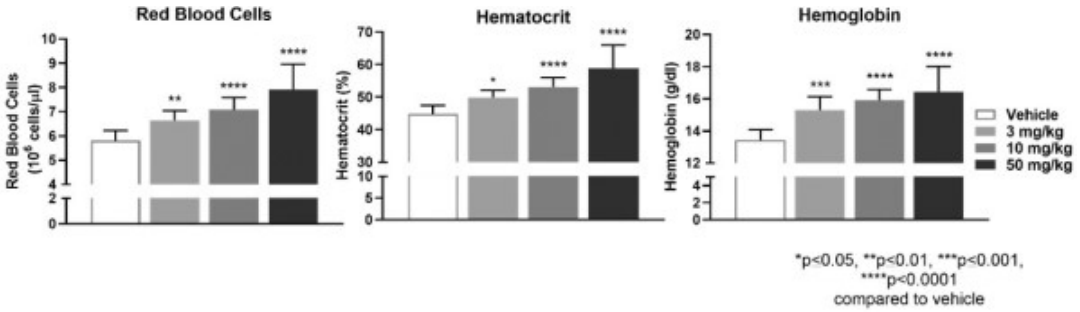


* P value ≤0.05; ** P value ≤0.01; NS = not significant

KER-050 also observed to increase red blood cells in non-human primates

We believe that our observations in preclinical studies of KER-050 in non-human primates indicate that the red blood cell effects of KER-050 also translated to higher-order species. In this study, cynomolgus monkeys received subcutaneous administration every other week for three months of either vehicle or doses of 3 mg/kg, 10 mg/kg or 50 mg/kg of KER-050. Hematology was measured at baseline and on Day 92. Red cell mass, including red blood cell number, hematocrit and hemoglobin were dose-dependently increased in the cohorts receiving KER-050. These data demonstrate the translatability of red blood cell, hematocrit and hemoglobin increases observed in preclinical studies of KER-050 from mice to non-human primates.

Increase in Red Blood Cells, Hematocrit and Hemoglobin in Cynomolgus Monkeys

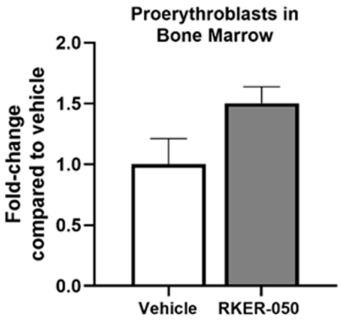


RKER-050 also observed to increase numbers of erythroid progenitors in mice

To evaluate the mechanism of action of RKER-050 in erythropoiesis, we collected and analyzed bone marrow from RKER-050-treated mice for erythroid progenitors. We observed a RKER-050-mediated increase in the

proerythroblast, or Pro-E, population in a flow cytometry analysis that used antibodies directed against cell surface markers to label-specific cell populations.

Increase in Overall Numbers of Proerythroblasts in Mice

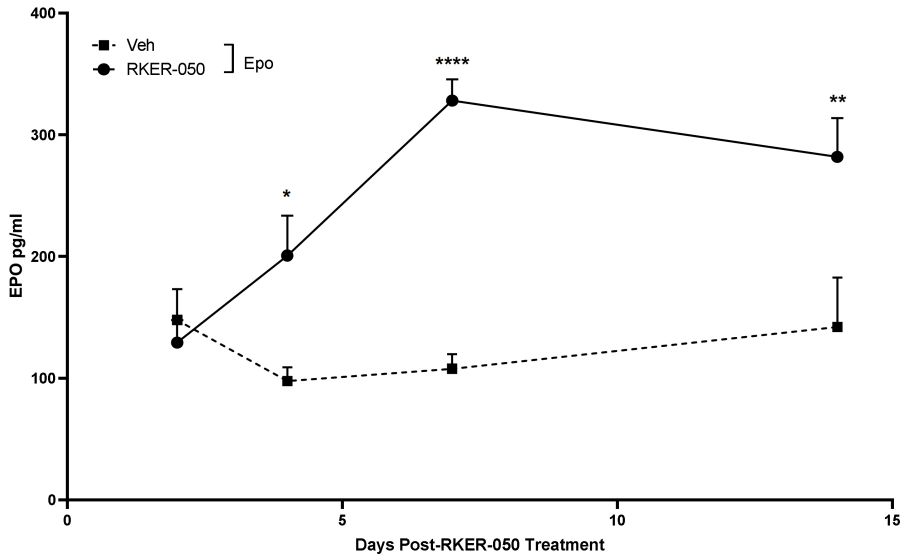


The rapid expansion of the Pro-E population also coincided with decreased numbers of erythroid burst-forming units and erythroid colony-forming units, the cells that give rise to Pro-E cells, which demonstrates that treatment with RKER-050 stimulated the erythroid burst-forming units and erythroid colony-forming units into erythroid differentiation. Since treatment with RKER-050 stimulated the earliest progenitors in the erythroid lineage to progress to maturation and increased the Pro-E pool, the first cells to start synthesis of hemoglobin, we believe KER-050 has the potential to affect the early stages of erythropoiesis.

RKER-050 also observed to increase serum erythropoietin and bone marrow erythropoietin receptor expression in mice

In a preclinical study conducted in mice, a single, subcutaneous 10 mg/kg dose of RKER-050 increased serum erythropoietin at days 4, 7 and 14 post-dose in mice. We believe the observed increase in erythropoietin could contribute to the durability in red blood cell production we observed in preclinical studies and supports the durability of the red blood cell increase we observed in our Phase 1 clinical trial of KER-050 in healthy post-menopausal women.

Observed Increase in Serum Erythropoietin in Mice



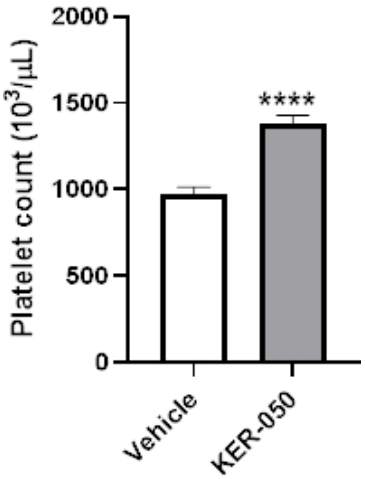
* P value ≤0.05; ** P value ≤0.01; **** P value ≤0.0001

Given that KER-050 increased early erythroid precursor cell pools in this preclinical study and its effect on upregulating serum erythropoietin, we believe KER-050 has the potential to treat patients with MDS that have hypocellular bone marrow. We believe the observed increases in serum erythropoietin in mice that were dosed with KER-050 support the potential of KER-050 as a therapy for patients with low serum erythropoietin across a diverse set of diseases, including chronic kidney diseases and polycythemia.

KER-050 observed to stimulate platelet release into circulation in wild-type mice

To evaluate the effect of KER-050 on blood cell types other than red blood cells, mice were administered a single, subcutaneous 7.5 mg/kg dose of KER-050 and had blood sampled and analyzed 4 days post-dose. Mice that received KER-050 were observed to have increased platelet counts compared to mice in the vehicle cohort.

Observed Increase in Platelet Count in Mice



**** P value <0.005

We believe that the findings from our preclinical studies and from our Phase 1 clinical trial of KER-050 in healthy post-menopausal women demonstrate the translation of biological action from rodents to humans. We also believe that data from our preclinical studies and clinical trials support that treatment with KER-050 has the potential to address ineffective hematopoiesis in diseases where multiple cytopenias arise from the blockage in progression of progenitor cells to mature blood cells, such as in MDS and myelofibrosis.

KER-047: For the Treatment of Anemia Arising from Iron Imbalance

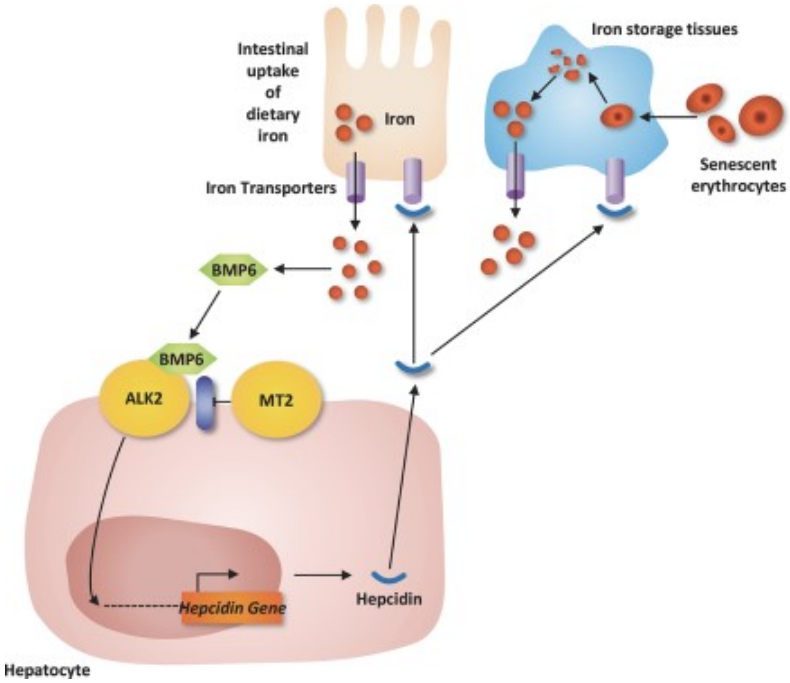
We are developing KER-047, our lead small molecule product candidate, for the treatment of anemia resulting from iron imbalance. We believe KER-047 is a potent and selective inhibitor of ALK2, a receptor whose excessive signaling is the underlying cause of the elevated levels of hepcidin, the key regulator of iron absorption and recycling, that leads to low iron bioavailability and anemia in a broad range of diseases. In August 2020, we announced the completion of our planned single and multiple ascending dose cohorts in a Phase 1 clinical trial of KER-047 in healthy volunteers, as well as the expansion of this trial to evaluate additional cohorts of healthy volunteers. We reported topline data from the planned cohorts of this trial in August 2020. In these cohorts, we observed dose-dependent increases in serum iron. We also observed increases in reticulocyte hemoglobin, which is a measure of hemoglobin content from newly-produced immature red blood cells, in the volunteers who received KER-047. One additional cohort of healthy volunteers was evaluated in the trial expansion. Data from this cohort supports the effect of KER-047 observed in the planned cohorts. We terminated the trial after determining that the data from this cohort, in addition to the data from the planned cohorts, were sufficient to inform the design of the expected Phase 2 clinical trials of KER-047, and expect to report topline data from this trial at a scientific conference by the end of 2020.

Hepcidin and Iron Homeostasis

Iron supply in the bone marrow is critical for erythropoiesis, as iron is an essential component of hemoglobin. Although iron is required for many functions in the body, including erythropoiesis, high iron levels are toxic, so circulating levels are regulated to avoid iron overload. To maintain this balance, absorption of dietary iron is tightly controlled and recycled iron is held in the liver and macrophages, which we refer to as the storage tissues, to be mobilized quickly when circulating iron levels are too low. These storage tissues also act to sequester away iron when levels are too high. Hepcidin, a hormone produced by the liver, is the key regulator of iron absorption and recycling, and controls both the recirculation of iron from storage tissues as well as the absorption of dietary iron from the intestine.

Hepcidin levels are upregulated through activation of the ALK2 receptor, which is a BMP receptor belonging to the broader TGF-ß family of proteins. Hepcidin levels are tightly regulated by liver cells through BMP6 signaling via ALK2. High serum iron triggers the expression of BMP6, which then acts to increase hepcidin expression, resulting in iron sequestration, decreased iron absorption and reduced serum iron. Hepcidin is controlled by a feedback loop, and serum hepcidin levels are inversely related to serum iron levels. This feedback loop prevents this system from shifting out of balance. The system is down regulated through the activity of matriptase-2, or MT-2, a cell surface protease, which is encoded by the TMPRSS6 gene. This protein reduces the ability of BMP6 to signal through ALK2. The below graphic illustrates a normal functioning of the negative feedback loop.

Regulation of Iron in the Body



Anemia Arising from Iron Imbalance, including Iron Deficiency Anemia and IRIDA

Failure to suppress ALK2 signaling can result in elevated hepcidin levels, which are associated with decreased dietary iron absorption, increased iron sequestration in storage tissues and low iron bioavailability in the bone marrow. These effects culminate in a shortage of serum iron, which leads to insufficient red blood cell production that manifests as mild to moderate anemia.

Iron deficiency anemia, or IDA, is a common form of anemia that is caused by patients not having enough iron to manufacture healthy red blood cells. IDA is associated with fatigue, lethargy, decreased quality of life, cardiovascular complications, hospitalizations and increased mortality. IDA is prevalent in many different patient

populations, including patients with IDA due to chronic kidney disease, chemotherapy-induced anemia and gastrointestinal diseases or disorders. It is estimated that approximately five million people in the United States have IDA and we believe that a small fraction of the patients who are diagnosed with IDA regardless of the underlying cause are currently being treated with intravenous, or IV, iron.

Additionally, high hepcidin levels can be the result of genetic disease. Iron-refractory iron deficiency anemia, or IRIDA, is a rare, inherited form of IDA that results in loss of function of MT-2, resulting in elevated ALK2 signaling and high hepcidin levels. Patients with IRIDA have the typical symptoms of anemia, including fatigue, weakness and shortness of breath, in addition to other symptoms associated with low iron. These symptoms are most pronounced during childhood, although they tend to be mild.

The prevalence of IRIDA worldwide is estimated to be less than one person in 1,000,000. IRIDA was first described in 1981 with the observation that patients with anemia were refractory to treatment with oral iron. However, the association of mutations in the TMPRSS6 gene with IRIDA was not identified until 2008, and genetic testing for IRIDA is not widely available. Furthermore, affected individuals usually have normal growth and development, so IRIDA is poorly diagnosed. All these factors contribute to an inability to accurately determine the prevalence of IRIDA.

Proinflammatory cytokines can also result in inappropriately high ALK2 signaling, increased hepcidin expression and anemia. Patients with chronic inflammation have mild to moderate anemia resulting from low serum iron that is driven by abnormally high hepcidin levels through sustained cytokine-mediated ALK2 activation. Anemia of inflammation is the second most common cause of anemia worldwide. The prevalence of anemia varies among different inflammatory rheumatic diseases. In the United States, approximately 1,000,000 people older than age 65 suffer from diseases of chronic inflammation, including rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis. Anemia with high hepcidin levels has also been reported in patients with primary myelofibrosis.

Limitations of Current Treatment Options for Anemia Arising from Iron Imbalance, including IRIDA

There are no current treatments that address the underlying cause of anemia arising from iron imbalance, including in patients with IDA associated with co-morbidities and in patients with IRIDA.

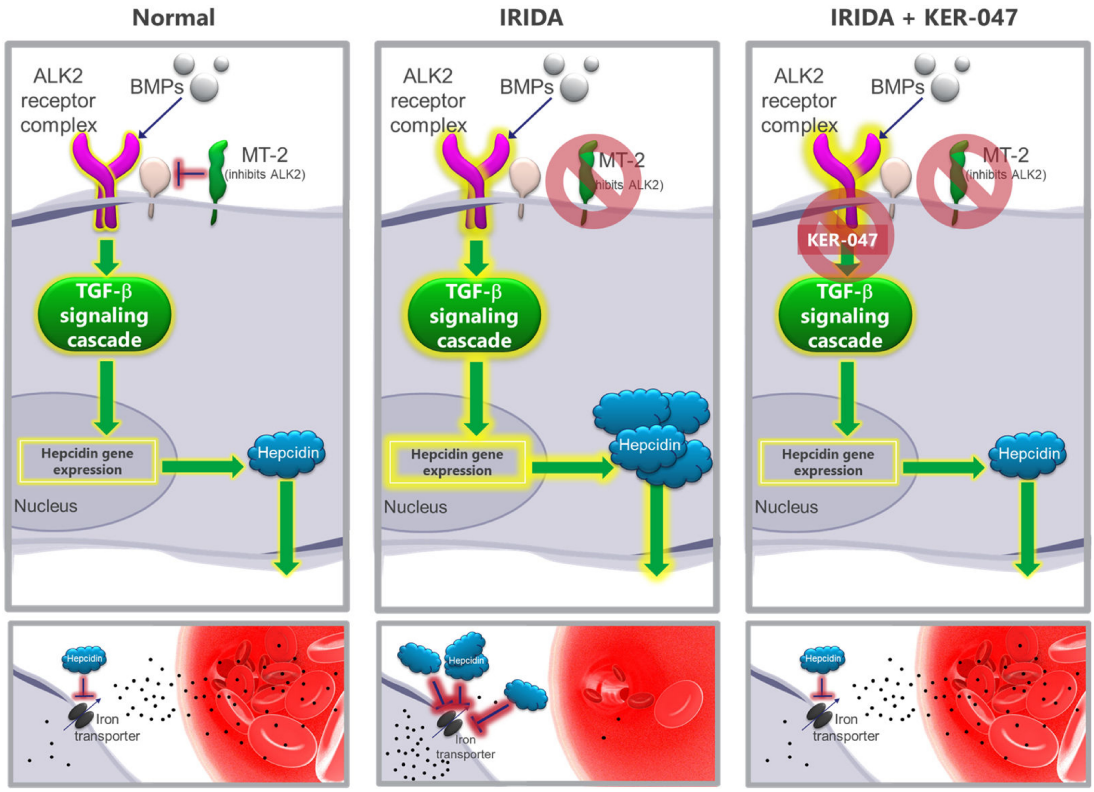
Currently, there are two common methods of iron therapy used to treat IDA: oral iron supplements and IV iron. While oral iron supplements are used as first-line iron replacement therapy for most patients, they are poorly absorbed and not well tolerated by some patients, which may adversely impact their effectiveness. The beneficial effect of oral iron supplements on increasing hemoglobin levels can require an extended treatment period, and, at times, treatment is inadequate to achieve the targeted hemoglobin levels. Conversely, iron administered by IV infusion allows larger amounts of iron to be delivered to patients in a shorter time frame, which can result in faster rises in hemoglobin levels. However, for patients with IDA associated with co-morbidities, neither of these treatments address the underlying cause of the disease. Additionally, these treatments can also cause mild side effects, such as constipation, diarrhea and cramping, and can increase the risk of very serious, life-threatening side effects, such as hypersensitivity reactions, opportunistic infections and the deposition of excess iron in organs in patients with co-morbidities such as chronic kidney disease.

Separately, patients with anemia due to ineffective erythropoiesis that require frequent red blood cell transfusions may have elevated levels of hepcidin with accompanying iron overload in multiple organ systems. This chronic iron overload can lead to multiple organ dysfunction, including in the liver, heart and endocrine. Accordingly, iron chelation therapy is used to reduce iron deposits in those organs. We believe that a treatment option that reestablishes normal iron homeostasis has the potential to benefit a broad range of patients, from patients with IDA to patients with anemia associated with iron overload.

Our Solution: KER-047

KER-047 is an orally-available small molecule ALK2 inhibitor designed to potently inhibit ALK2 signaling, with high selectivity for ALK2 relative to other structurally-similar TGF-ß receptors as well as other kinase families.

Mechanism of Action of KER-047



We believe that KER-047 has the potential to address the underlying cause of diseases arising from iron imbalance, including IDA, IRIDA and iron overload, by suppressing ALK2 signaling to normalize hepcidin expression and mobilizing iron out of tissues. We believe this effect will result in increased iron bioavailability, resulting in restoration of the production of red blood cells and a reversal of anemia in patients with IDA and patients with IRIDA. By ameliorating anemia arising from iron imbalance, we believe KER-047 can potentially eliminate the need for excessive supplementary iron or IV iron treatments and avoid the adverse events associated with those treatment options. In addition, we believe KER-047, if approved, has the potential to be beneficial in diseases of iron overload by mobilizing excess iron being stored in tissues into the serum. By ameliorating the excess iron in tissues, we believe KER-047 can potentially eliminate or reduce the need for phlebotomy and/or treatment with iron chelators, while allowing patients to avoid the adverse events associated with these treatments and providing benefit to patients where the current treatment options are largely ineffective.

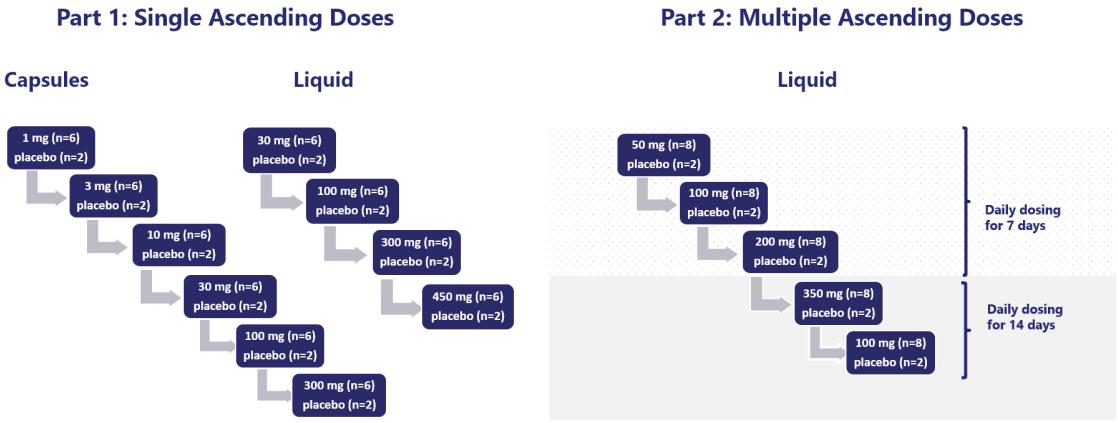
In August 2020, we announced the completion of our planned single and multiple ascending dose cohorts in a Phase 1 clinical trial of KER-047 in healthy volunteers, as well as the expansion of this trial to evaluate additional cohorts of healthy volunteers. One additional cohort of healthy volunteers was evaluated in the trial expansion. We terminated the trial after determining that the data from this cohort, in addition to the data from the planned cohorts, were sufficient to inform the design of the expected Phase 2 clinical trials of KER-047, and expect to report topline data from this trial at a scientific conference by the end of 2020. We also expect to commence two Phase 2 clinical trials of KER-047, one in patients with IDA and one in patients with IRIDA, in

2021. Additionally, we intend to develop KER-047 as a potential treatment for patients who manifest anemia caused by high hepcidin levels as a secondary consequence of more common diseases.

Expanded Phase 1 Clinical Trial

We conducted a randomized, double-blind, placebo-controlled, two-part Phase 1 clinical trial to evaluate single and multiple ascending doses of KER-047 in healthy volunteers. The primary objectives of this trial are to assess safety, tolerability and pharmacokinetics of KER-047. The trial design for the planned single and multiple ascending dose cohorts of KER-047 is summarized in the figure below.

Phase 1 Clinical Trial Design



Observed tolerability data

There were no serious adverse events reported in this expanded Phase 1 clinical trial. The most common adverse events observed in healthy volunteers in this expanded trial were abdominal discomfort, chills, decreased appetite, diarrhea, dizziness, fatigue, gastroenteritis, headache, lymphopenia, myalgia, nausea, neutropenia, pyrexia, rhinorrhea, tonsilitis, upper abdominal pain and vomiting.

Rapid mobilization of iron stores resulted in increased reticulocyte hemoglobin content of newly-produced immature red blood cells

In this expanded Phase 1 clinical trial, we observed rapid and dose-related increases in serum iron and transferrin saturation in the volunteers who received KER-047. We also observed a reduction in hepcidin at each dose level tested in Part 2 of this expanded trial, which we believe is consistent with KER-047's mechanism of action. Importantly, we believe the iron mobilization led to increased iron bioavailability for incorporation into reticulocyte hemoglobin, a measure of hemoglobin content from newly-produced immature red blood cells. These erythroid precursors potentially would continue maturation into hemoglobin-rich red blood cells.

We also observed decreases in lymphocytes following peak increases in serum iron in this expanded trial, which we believe is consistent with KER-047's mechanism of action and suggestive of depletion of tissue iron.

We believe the data from this expanded Phase 1 clinical trial support the potential for KER-047 to be developed as a treatment for diseases arising from iron imbalance.

Observed reductions in total cholesterol

Reductions in total cholesterol, low-density lipoproteins, or LDL, and high-density lipoproteins were observed in Part 2 of this expanded trial. The reductions in total cholesterol and LDL were achieved rapidly with a mean reduction of greater than 20% at the highest dose, following seven days of dosing.

Clinical Development Strategy

We recently completed the planned single and multiple ascending dose cohorts in this trial. Based upon preliminary analysis, we expanded the Phase 1 trial to evaluate additional cohorts of healthy volunteers. One additional cohort of healthy volunteers was evaluated in the trial expansion. We terminated the trial after determining that the data from this cohort, in addition to the data from the planned cohorts, were sufficient to inform the design of the expected Phase 2 clinical trials of KER-047, and expect to report topline data from this trial at a scientific conference by the end of 2020. We expect to commence separate Phase 2 clinical trials in patients with IDA and in patients with IRIDA in 2021.

Preclinical Data

KER-047 was observed in preclinical studies to be a potent and highly selective ALK2 inhibitor and to change serum iron levels. Specifically, KER-047 demonstrated in these studies:

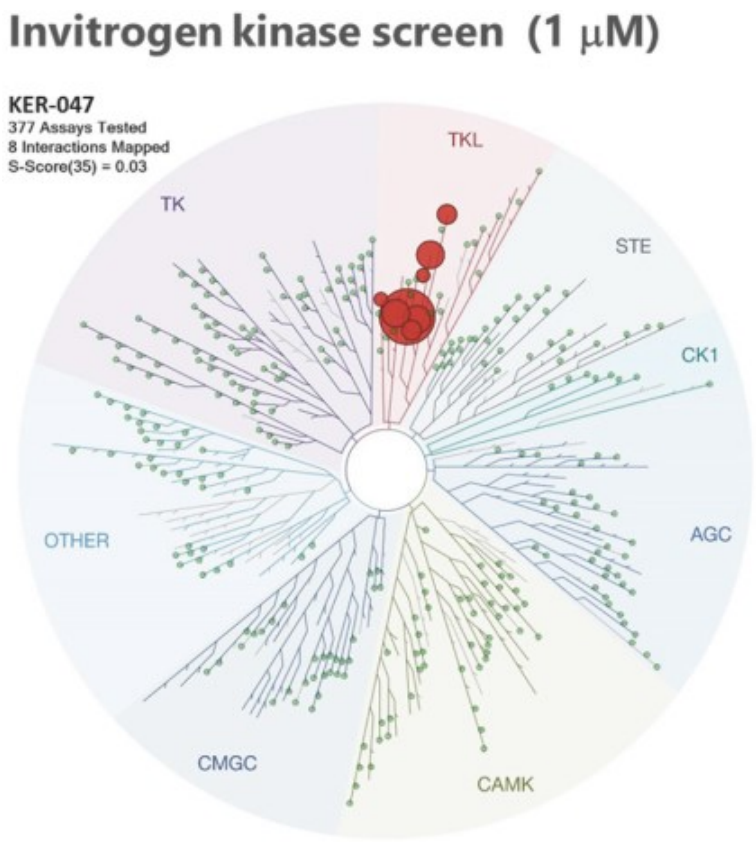
- selectivity for ALK2 compared to other structurally-related TGF-ß and non-TGF-ß kinases;
- increased serum iron levels in rat studies; and
- reversal of high hepcidin levels and low hemoglobin levels in a mouse model of IRIDA.

KER-047 observed to be a potent and highly selective ALK2 receptor inhibitor in a biochemical assay

In standard biochemical kinase screenings, KER-047 exhibited low nanomolar potency for ALK2. Under the conditions of this assay, KER-047 exhibited at least an eight-fold selectivity over the other structurally-related TGF-ß kinases. In a 370-member kinase panel, only two non-TGF-ß kinases were inhibited less than

75% at a KER-047 concentration of 1 µM. We believe these preclinical data further support the potency and selectivity of KER-047 for the ALK2 domain.

Highly Selective ALK2 Receptor Inhibitor



The kinase selectivity of KER-047 is shown in the dendrogram above. Compounds were screened at 1 µM against a panel of over 370 kinases and disease-relevant mutants. Each branch of the dendogram represents an individual human kinase. Kinases bound by the compound are indicated by red circles on the kinome tree. The degree of binding corresponds to the size of the circle. As illustrated by the largest red circle in the above graphic, KER-047 was observed to be a potent ALK2 inhibitor and a weak inhibitor of other members of the TGF-ß family of receptors.

In cell-based assays that more directly tested the functional ability of KER-047 to suppress receptor signaling, KER-047 exhibited low nanomolar potency. In assays evaluating the effect of KER-047 on receptors with the highest structural homology to ALK2, KER-047 had at least 20-fold selectivity for ALK2, compared to ALK1 and ALK5, which have 77% and 65% homology to ALK2, respectively.

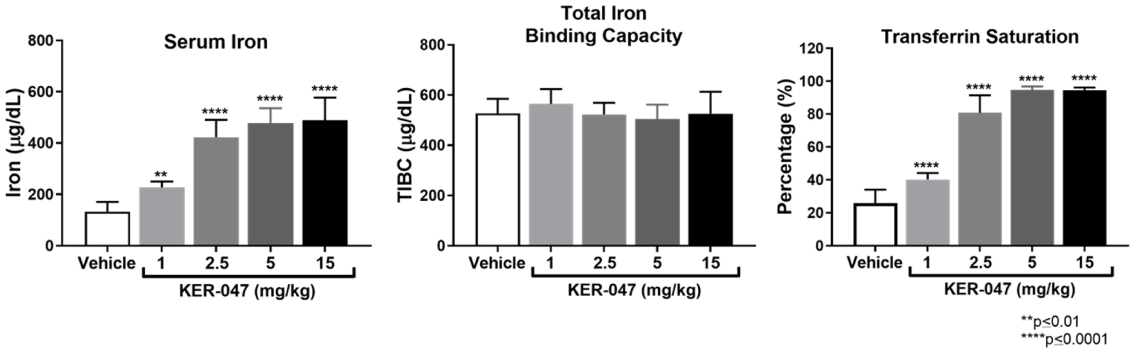
KER-047 inhibition of ALK2 signaling resulted in increased serum iron and transferrin saturation in multiple animal models

We believe that data from preclinical studies support a link between ALK2 signaling, hepcidin expression and serum iron across multiple preclinical species in both healthy and disease models. Serum iron is an indicator of whether there is adequate iron available in the body. Total iron binding capacity is the measure of the maximum amount of iron that can be bound by transferrin, an iron-binding protein, and is a surrogate measurement of serum transferrin levels. Transferrin saturation is calculated by dividing serum iron by total iron binding capacity

and is an indicator of how well the body is transporting the iron in blood. Taken together, these values are an indication of the state of iron balance in the body.

We evaluated serum iron, total iron binding capacity and transferrin saturation in Sprague-Dawley rats that received daily, oral administration of either vehicle or doses of 1 mg/kg, 2.5 mg/kg, 5 mg/kg or 15 mg/kg of KER-047 for three months. Rats that were treated with KER-047 were observed to have a dose-dependent increase in serum iron levels and a concomitant increase in transferrin saturation, with no change in total iron binding capacity.

Increased Serum Iron, Total Iron Binding Capacity and Transferrin Saturation in Rats

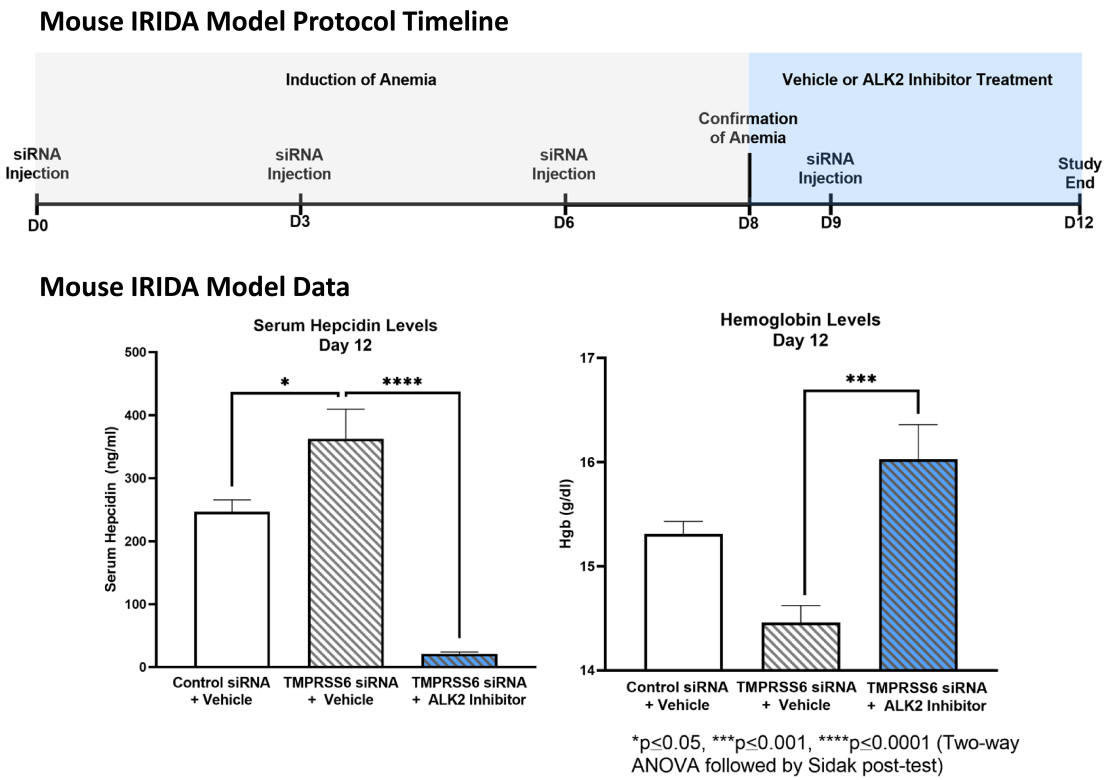


These data demonstrate that ALK2 inhibition resulted in increased serum iron and that KER-047 acts by releasing iron into blood without altering the expression or functionality of iron binding proteins. We believe that these data demonstrate that treatment with KER-047 has the potential to alter ALK2 signaling and release iron from storage tissue for transport to other tissues, including in the bone marrow.

Treatment with an ALK2 inhibitor closely related to KER-047 was also observed to reverse anemia in a mouse model of IRIDA. To generate this mouse model, we used an siRNA directed against TMPRSS6, the same gene that is defective in patients with IRIDA, to render the mice TMPRSS6-deficient. We confirmed that mice receiving the TMPRSS6 siRNA had a greater than 85% reduction of target gene expression relative to the control siRNA cohort. This model recapitulated the increased hepcidin levels and reduced hemoglobin that are characteristic of patients with IRIDA. Treatment of the mice receiving the TMPRSS6 siRNA with an ALK2 inhibitor normalized levels of both hepcidin gene expression and hemoglobin levels compared to the control

siRNA cohort receiving vehicle treatment, which we believe indicates that ALK2 inhibition can reverse anemia resulting from iron imbalance.

Serum Hepcidin and Hemoglobin Levels in Mice with siRNA-induced IRIDA



The sequence of the ALK2 receptor has been highly conserved through evolution, with greater than 98% amino acid sequence homology between mice and humans. Likewise, the finding that the mouse models with changes in ALK2 signaling recapitulate human disease also provides evidence that the function of the ALK2 receptor is conserved across species. For example, knockdown of the TMPRSS6 gene results in a phenocopy of the disease observed in patients with IRIDA. We believe that the conservation of biology provides confidence that treatments that are efficacious in preclinical models will have similar effects in humans.

Our Fibrodysplasia Ossificans Progressiva Program

We are also developing KER-047 for the treatment of fibrodysplasia ossificans progressiva, or FOP. FOP is a rare genetic disease resulting from gain-of-function mutations in the ALK2 receptor. In patients with FOP, soft tissue, including muscles and tendons, develops normally, but remodels into bone spontaneously or after injury. There are currently no approved treatments for FOP. We believe KER-047 has the potential to prevent progression of disease in these patients by normalizing ALK2 signaling.

Fibrodysplasia Ossificans Progressiva

FOP results from single amino acid mutations in the ALK2 receptor that result in gain-of-function activity of the receptor. An estimated 97% of patients with FOP have an R206H mutation that results in excessive ALK2 receptor signaling. Multiple processes drive this excessive signaling. The ALK2/R206H receptor is inappropriately activated by activins A and B, hyperresponsive to the endogenous BMP ligands and can be active in the absence of ligands. These changes all result in increased kinase-mediated signaling and upregulation of bone-forming cellular activity, such as heterotopic ossification.

Heterotopic ossification in patients with FOP can occur spontaneously or can be triggered by soft tissue trauma, such as from immunizations, falls, surgery or viral illnesses. The bony lesions from heterotopic ossification are painful and restrict movement. These lesions are permanent and their accumulation leads to progressive loss of function and immobility, eventually resulting in patients becoming wheelchair-dependent, making independent living difficult. Patients can have additional morbidity due to severe weight loss resulting from bone developing in and essentially locking the jaw, as well as respiratory problems due to constriction of the rib cage. Additionally, development of pneumonia and heart failure results in a high mortality rate, with a median age of death of 40 years. The International Fibrodysplasia Ossificans Progressiva Association estimates that there are 3,500 people worldwide with FOP, with approximately 800 patients identified. There are 285 known cases in the United States.

Limitations of Current Treatment Options for FOP

There are no therapies approved to treat FOP. Patients are administered anti-inflammatory agents to minimize tissue damage and alleviate pain, but these treatment options do not reduce or prevent bone formation. Surgical removal of the heterotopic ossification is performed in extreme cases, such as when the bony lesion is hindering jaw movement. However, this intervention only provides temporary benefit, as bone that is surgically removed is quickly replaced by a similar volume of new bone in its place.

Our Solution: KER-047

KER-047 is designed as an ALK2 inhibitor that is also designed to inhibit the ALK2/R206H mutant receptor, which we believe presents the potential to address the underlying cause of FOP as well as prevent the development of new, and the expansion of existing, heterotopic ossification. Additionally, we believe that KER-047 has the potential to prevent the regrowth of bone after surgical resection and *de novo* bone formation resulting from surgery-induced trauma.

FOP treatments currently in development, such as palovarotene, were observed to hamper the healing process in preclinical studies. We believe treatment with KER-047 would not interfere with a patient's ability to undergo and recover from surgery. Additionally, treatment with palovarotene has been observed in a Phase 2 clinical trial to cause premature closure of growth plates in pediatric patients. ALK2 signaling is not required for normal skeletal growth and development, and in our preclinical studies, we did not observe changes to normal bone growth when treating mice with dose levels of KER-047 that resulted in a reduction in the amount of heterotopic ossification. Based on these data, KER-047 would not be expected to affect normal skeletal development and could be used to treat patients with FOP of all ages.

Following the completion of our expected Phase 2 clinical trial of KER-047 in patients with IDA, we plan to commence a Phase 2 clinical trial in patients with FOP.

Preclinical Data

We have generated compelling biochemical and preclinical data that we believe demonstrated proof-of-mechanism of KER-047 for the treatment of FOP. Specifically, KER-047 demonstrated in these studies:

- potent ALK2/R206H mutant receptor inhibitor;
- dose-dependent reduction in the formation of heterotopic ossification in multiple mouse models; and
- no shortening of long bones in mice receiving the ALK2 inhibitor.

KER-047 observed to be a potent ALK2 receptor inhibitor and ALK2/R206H mutant receptor inhibitor

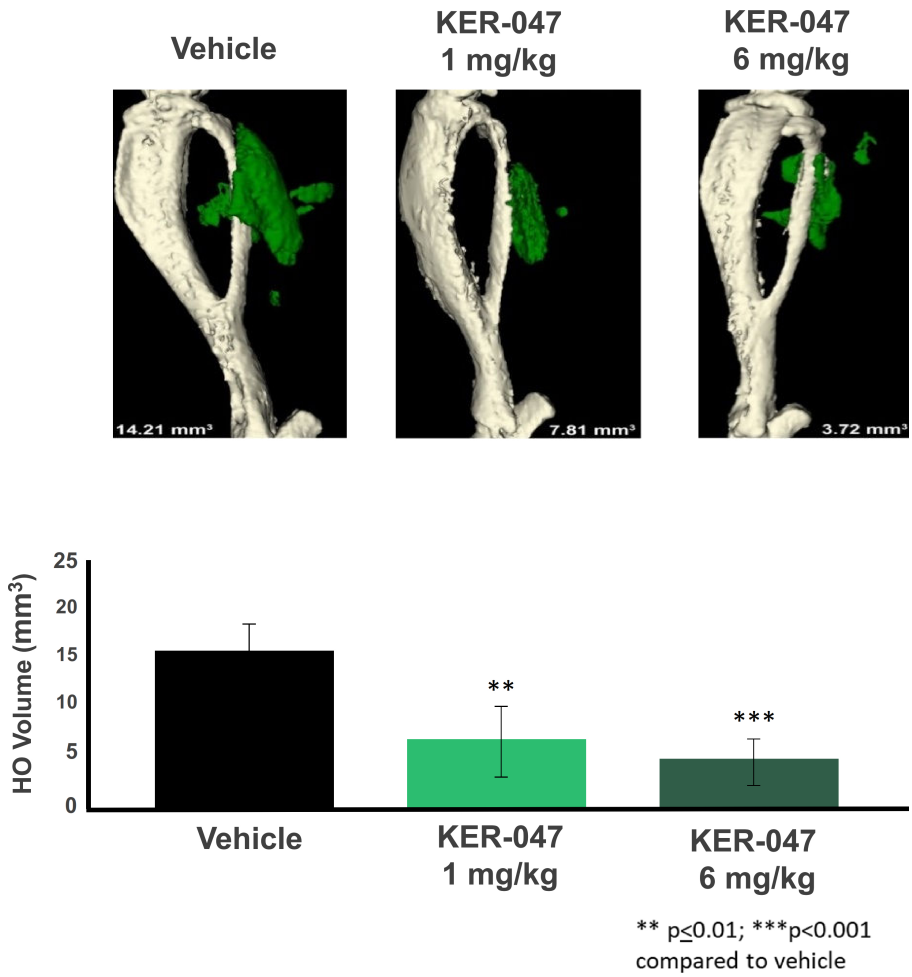
In an *in vitro* assay, KER-047 was observed to be a potent ALK2 receptor inhibitor. In cell-based reporter assays, KER-047 also exhibited low nanomolar potency against the ALK2/R206H mutant receptor.

KER-047 inhibited ALK2 signaling and was associated with reduced bone formation in a mouse model of heterotopic ossification

In patients with FOP, heterotopic ossification is driven by excessive signaling through a mutated ALK2 receptor. We evaluated treatment with KER-047 in an R206H mouse model of FOP and observed a dose-dependent reduction in heterotopic ossification. In our preclinical study, mice were treated with either vehicle or doses of 1 mg/kg or 6 mg/kg of KER-047, dosed daily by oral gavage, starting three days prior to mice receiving the pinch injury and continuing through 14 days post-injury. Micro-CT scans were analyzed for the presence of heterotopic ossification lesions in muscle. In mice with the ALK2/R206H mutant receptor receiving KER-047, a

statistically significant, dose-dependent reduction in the formation of heterotopic ossification after pinch injury was observed.

Reduced Formation of Heterotopic Ossification in a Mouse Model of FOP Representative MicroCT Images



Treatment with a selective ALK2 inhibitor did not affect skeletal development in young mice

Third-party reports have described how treatment of young mice with palovarotene, a RAR-gamma agonist, resulted in growth plate closure in the normal skeleton, which led to a shortening of the long bones. We dosed two-week old mice with a potent ALK2 inhibitor closely related to KER-047 and measured changes in length of the long bones. While ALK2 inhibition failed to alter the length of the long bone, we observed a statistically significant shortening of the long bones in mice treated with palovarotene.

Our Preclinical Pipeline

KER-012

KER-012 is a ligand trap comprised of a modified ligand-binding domain of ActRIIB that is fused to the portion of the human antibody known as the Fc domain. KER-012 is designed to bind to and inhibit the signaling of TGF-ß ligands, including activin A and activin B, which are key regulators of bone remodeling that act to suppress bone growth, to potentially increase bone mass. We believe that KER-012 has the potential to increase the signaling of BMP pathways through this inhibition of activin A and activin B signaling, and

consequently treat diseases such as PAH that are associated with reduced BMP signaling due to inactivating mutations in the BMP receptors. We are developing KER-012 for the treatment of disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta, and for the treatment of pulmonary arterial hypertension, or PAH.

Osteoporosis

Osteoporosis is a highly prevalent disease characterized by low bone mineral density and deterioration of bone structure, which leads to an increase in bone fractures. It is estimated that more than 200 million people worldwide, including approximately 30% of all post-menopausal women in the United States and Europe, suffer from osteoporosis. It is also estimated that 50% of women and 20% of men over the age of 50 will suffer at least one osteoporosis-related fracture in their remaining lifetime. These fractures can lead to increased morbidity and mortality. With the number of individuals over the age of 50 expected to increase, the incidence of osteoporosis-related fractures is predicted to double or triple in the upcoming decades.

Limitations of Current Treatment Options for Osteoporosis

Patients with osteoporosis are generally treated with anti-resorptive agents and anabolic agents. Anti-resorptive agents act to prevent further bone loss by inhibiting the breakdown of bone, while anabolic agents stimulate bone formation to build new, high-quality bone.

Bisphosphonate anti-resorptive agents, including Aredia (pamidronate), Fosamax (alendronate) and Reclast (zoledronic acid), are the current standard of care, and these treatments inhibit the cells that resorb or take away bone. However, bisphosphonates have limited efficacy for non-vertebral fractures, and gains in bone mineral density have been observed to plateau after a few years of treatment. Additionally, bisphosphonate use has been associated with infrequent but serious adverse events, such as osteonecrosis of the jaw and atypical femoral fractures. These side effects, although rare, have created increasing concern among physicians and patients. Accordingly, the number of bisphosphonate prescriptions has declined over 50% in the last decade and physicians are seeking alternatives.

There are several alternatives to bisphosphonates that are approved for the treatment of osteoporosis, including anti-resorptive agents and anabolic agents. The most potent anti-resorptive product that is approved for treatment is Prolia (denosumab). Given twice a year via subcutaneous injection by a physician, Prolia increases bone density and reduces hip, spine and non-vertebral fractures. However, in the past five years, there have been numerous reports about fractures, especially those of the spine, occurring after the cessation of Prolia, which we believe has caused many patients with osteoporosis to refrain from commencing treatment with Prolia.

Anabolic therapies approved for treatment of osteoporosis include Forteo (teriparatide) and Tymlos (abaloparatide). Delivered by daily subcutaneous injection, these products have been observed to improve bone density and reduce vertebral fractures, but have limited evidence for reduction of hip fracture, which is frequently a debilitating fracture for patients. Additionally, use of these products is restricted to two years and their labels include a black-box warning regarding the occurrence of bone cancer in rats treated with Forteo, which is a key deterrent to using these products for many patients.

Evenity (romosozumab-aqqg), an anabolic therapy, increases bone formation briefly while also reducing bone resorption. The reason for the short-term nature of the anabolic effect is unclear. Evenity is delivered via two subcutaneous injections monthly at a doctor’s office, with use restricted to 12 months. Although Evenity exhibited robust anti-fracture efficacy and large gains in bone mineral density in a third-party Phase 3 clinical trial, the Evenity label includes a black-box warning that the product may increase the risk of heart attack, stroke or death from a cardiovascular event.

We believe there is a large unmet need for patients with osteoporosis, as existing therapies have shortcomings in efficacy, tolerability, convenience and safety. Given these shortcomings, we believe there is a significant market opportunity for an anabolic agent such as KER-012, which is designed to be a potent and selective inhibitor of certain TGF-ß ligands, including activin A and activin B, that are key regulators of bone remodeling that act to suppress bone growth. Additionally, with a growing population of older adults, the number of patients with osteoporosis is predicted to expand in the coming years.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a group of genetic disorders that mainly affect the bones. People with osteogenesis imperfecta have bones that fracture easily, often from mild trauma or with no apparent cause. Osteogenesis imperfecta affects approximately one out of every 10,000 to 20,000 people worldwide, while an estimated 25,000 to 50,000 people in the United States are living with the condition.

Limitations of Current Treatment Options for Osteogenesis Imperfecta

There are no approved therapies for the treatment of osteogenesis imperfecta in the United States or the European Union. Current treatment of osteogenesis imperfecta is directed towards the management of fractures with casting or surgical fixation, followed by physical therapy. Preventative surgeries, such as intramedullary, or in-bone, nailing fixation, in which a permanent nail or rod is placed into the center of the bone, are also undertaken. However, these surgical options do not treat the underlying cause of osteogenesis imperfecta. Additionally, bisphosphonates, which are not approved for osteogenesis imperfecta, are commonly used off-label in children. A meta-analysis of randomized trials demonstrated that there was no evidence that current treatments, including bisphosphonates, reduce fracture risk in patients with osteogenesis imperfecta. Controlled clinical trials also showed no improvement in bone pain, a key disability in children with osteogenesis imperfecta. Additionally, we are not aware of any long-term clinical trials demonstrating a reduction in fractures in adults, and the effect of long-term therapy with these existing products remains unclear.

Pulmonary Arterial Hypertension

PAH is a debilitating disorder characterized by elevated pulmonary vascular resistance due to severe constriction and progressive obliteration of the pulmonary vessels. PAH results in diminished oxygenation, impaired cardiac output and symptoms stemming from overload of the right ventricle, such as shortness of breath, fatigue, fainting, chest pain, palpitations and swelling of extremities and abdomen. We estimate that in the United States there are 750 to 2,000 new cases of PAH each year and 10,000 to 20,000 individuals living with this condition. Despite current treatment options, survival with PAH remains only slightly above 50% at five years, with mortality typically resulting from right ventricle failure.

Loss-of-function mutations in the gene encoding the BMP type II receptor, or BMPR2, are present in over 70% of cases of heritable PAH, or HPAH, while loss-of-function mutations in certain BMPR2 co-receptors are present in other cases of HPAH and idiopathic PAH. Histology and gene expression studies from the lungs of human and experimental PAH showed diminished BMPR2 expression and BMP signaling even in the absence of loss-of-function mutations, as well as enhanced TGF-ß signaling. Consistent with an imbalance in the signaling of these families of ligands, it was recently found that PAH due to cirrhosis and portal hypertension is marked by a severe deficiency of circulating BMP9, while circulating TGF-ß, activin and growth differentiation factor, or GDF, ligands were found to be increased in PAH, even in the absence of causative mutations. Multiple experimental third-party models also demonstrated the efficacy of augmenting BMP signaling or suppressing TGF-ß, activin or GDF signaling, which we believe supports the notion that imbalanced homeostatic BMP and pathogenic TGF-ß, activin and GDF signaling drive the development and progression of pulmonary vascular disease.

Limitations of Current Treatment Options for PAH

All of the currently-approved therapies for PAH are vasodilators, which are medications that dilate blood vessels. These vasodilators fall into one of three categories: (i) prostanoids, which are agonists of the prostacyclin signaling pathway; (ii) endothelin receptor antagonists, or ERAs; or (iii) (a) phosphodiesterase 5 inhibitors, or PDE5i, which are agents that enhance nitric oxide metabolism, or (b) soluble guanylate cyclase activators, which cause downstream cGMP signaling.

One common approach to treating early-stage or mild PAH is an oral combination therapy using ERA and PDE5i medications. More severe PAH generally requires the addition of prostanoid, via oral or inhaled administration, while advanced PAH typically requires continuous parenteral administration. Each of these individual therapies may modestly improve a patient's functional status and in some cases survival, but is limited by systemic hypotension, systemic side effects and tachyphylaxis, which is an acute, sudden decrease in response to a product after its administration. Additionally, combination therapy is limited by the combined

side effect profiles. Although existing treatments may modestly slow the progression of PAH, none appear to halt or reverse the disease's progression.

While the key physiologic and pathologic features of PAH include vasoconstriction, scar tissue and vascular smooth muscle cell proliferation and inflammation, the main pharmacological effect for all currently approved therapies is believed to be vasodilation. Accordingly, we believe there is a significant unmet need for a treatment that primarily targets the proliferative pathological processes and can be used alone or in combination with other PAH therapies. We believe that potent therapies that do not exhibit tachyphylaxis, are orally bioavailable or do not require continuous infusion therapy would have advantages over the currently available treatments for PAH.

Therapies that arrest pulmonary vascular remodeling could have a long-term clinical stabilizing effect in PAH, or reverse vascular obliteration. We believe that KER-012 has the potential to increase the signaling of BMP pathways through the inhibition of activin A and activin B signaling, and consequently treat diseases such as PAH that are associated with reduced BMP signaling due to inactivating mutations in the BMP receptors.

Preclinical Data

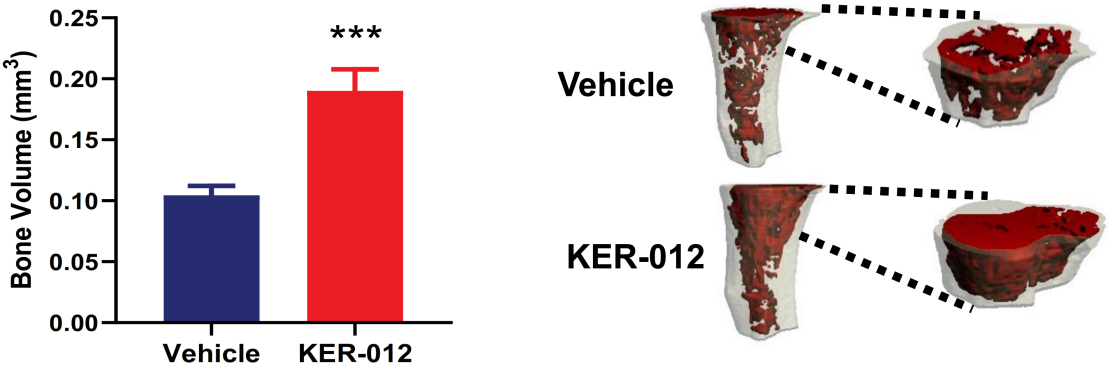
We have generated preclinical data that we believe demonstrated proof-of-mechanism of KER-012 for the treatment of disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta, and for the treatment of PAH. Specifically, in preclinical studies, KER-012:

- showed high affinity for and potent inhibition of ligands involved in the regulation of bone homeostasis;
- lacked binding to BMP9, a ligand critical in vascular remodeling, vascular stability and vascular quiescence;
- increased bone mineral density and trabecular bone volume in wild-type mice and mice with established osteoporosis; and
- did not increase red blood cell production in cynomolgus monkeys.

KER-012 targeted ligands that signal through ActRIIA and ActRIIB in preclinical studies

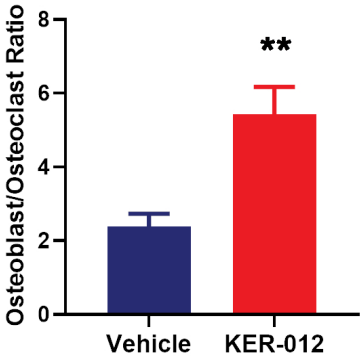
KER-012 is a modified ActRIIB ligand trap that contains sequences from both wild-type ActRIIB and wild-type ActRIIA. In preclinical studies, KER-012 bound to and inhibited multiple ligands that signal through these cell surface receptors, including activin A, activin B and growth differentiation factor 11. These ligands are key regulators of bone remodeling that act to suppress bone growth. BMP9 is a ligand capable of signaling through the ActRIIB and bone morphogenetic receptor II. Inhibition of BMP9 results in disruption of vascular remodeling, which can lead to the development of epistaxis and telangiectasias. KER-012 did not bind BMP9 or inhibit BMP9 signaling in preclinical studies. Consequently, we believe KER-012 has the potential to avoid negative effects on vascular remodeling.

Treatment with KER-012 increased bone mineral density



*** P value <0.001

In preclinical studies conducted in wild-type mice, twice weekly intraperitoneal 20 mg/kg dosing of KER-012 increased bone mineral density compared to vehicle-treated mice 31 days post-treatment. Additionally, we observed that treatment with KER-012 statistically significantly increased trabecular bone formation and mineral apposition rate, which we believe is consistent with an anabolic effect on bone.



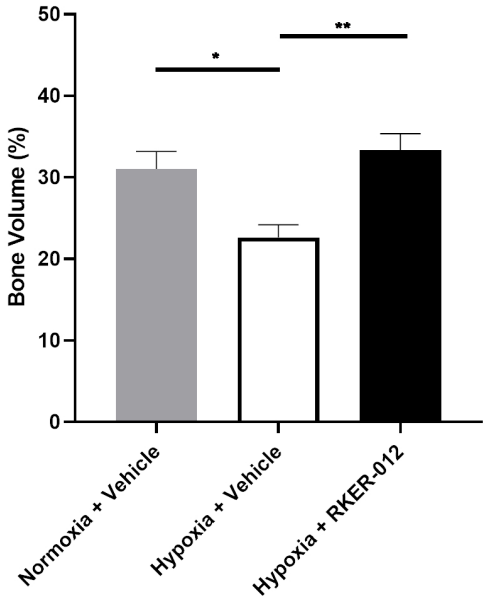
** P value <0.01

In a separate preclinical study, we observed that treatment with KER-012 increased the ratio of osteoblasts, which are bone forming cells, to osteoclasts, which are bone resorbing cells, which further supports that KER-012 acts via an anabolic effect on bone. We also observed in preclinical studies conducted in mice with established osteoporosis that twice weekly intraperitoneal 20 mg/kg dosing of KER-012 increased bone mass compared to vehicle-treated mice 46 days post-treatment.

Treatment with RKER-012 prevented cardiac hypertrophy in a rat model of PAH

We combined administration of SUGEN5416, a tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1/2, with exposure to chronic hypoxia to recapitulate the biology in PAH. In this model, remodeling of the arterial wall results in wall thickening, increased arterial pressure and impairment of heart function through a thickening of the right ventricle. Treatment with twice weekly subcutaneous 10 mg/kg dosing of the rodent version of KER-012, or RKER-012, was observed to protect against a thickening of the right ventricular wall, which we believe demonstrates that KER-012 has the potential to treat PAH.

Treatment with RKER-012 prevented bone loss from hypoxia in the rat model of PAH



* P value <0.05; ** P value <0.01

In the rat model of PAH, chronic hypoxia induced a catabolic state that resulted in wasting of tissue, including bone and muscle. Treatment with a subcutaneous 10 mg/kg dose of RKER-012 was observed to prevent bone loss in the rat model of PAH.

CKER-012 did not increase red blood cells in non-human primates

In a preclinical study, cynomolgus monkeys received subcutaneous administration every other week for one month of either vehicle or a 10 mg/kg dose of CKER-012, a monkey form of KER-012 comprised of the same modified ActRIIB fused to a cynomolgus Fc that has a ligand binding profile similar to that of KER-012. We measured hematology at baseline and on Day 35. Changes in red blood cells, hematocrit and hemoglobin over the 35-day study were not statistically significantly different compared to changes observed in the vehicle-treated cohort. Based on these findings that CKER-012 did not increase red blood cell production in monkeys, we believe KER-012 has the potential not to increase red blood cell production in humans.

Based on the findings from our preclinical studies, we believe KER-012 has the potential to treat disorders associated with bone loss, such as osteoporosis and osteogenesis imperfecta. Additionally, inhibition of BMP9 signaling can result in endothelial cell apoptosis, remodeling and arterial occlusion in diseases such as PAH. We believe that KER-012 has the potential to increase the signaling of BMP pathways through this inhibition of activin A and activin B signaling, and consequently treat diseases such as PAH that are associated with reduced BMP signaling due to inactivating mutations in the BMP receptors.

Our Proprietary Discovery Approach

We believe, based on our previous experience with ActRII ligand traps using the endogenous and wild-type sequences, that observations in preclinical rodent models have the potential to translate to humans in the clinic. Specifically:

- Wild-type ActRIIA-Fc was associated with increased bone growth and red blood cell production in rodents and non-human primates. In a third-party clinical trial of ActRIIA-Fc, increased bone mineral density and red blood cell production was reported in healthy post-menopausal women. In this clinical trial, it was also reported that lower doses elicited the effect on red blood cells compared to bone, and

thus, the dominant effect on red blood cell production prevented development in diseases with bone loss.

- In third-party preclinical studies in rodents and non-human primates, ActRIIB-Fc was associated with increased bone mineral density and lean muscle mass, but was not associated with changes in red blood cells. However, ActRIIB-Fc was also observed to cause nose and gum bleeding, which we believe is due to its effect of disrupting normal vascular remodeling. BMP9 signaling is required for normal vascular remodeling, but is not involved in regulation of muscle or bone tissues. ActRIIB-Fc potently inhibits BMP9 signaling, which is the mechanism behind the bleeding events observed with ActRIIB-Fc treatment.

We have developed a proprietary library of ActRII ligand traps by combining sequences from ActRIIA and ActRIIB. We have engineered molecules that are designed to have the therapeutic properties of either or both parent molecules without the dose-limiting effect on red blood cells observed with ActRIIA-Fc or the negative effect on blood vessels observed with wild-type ActRIIB-Fc. Our ActRII program has produced a broader pipeline of engineered ligand traps and currently contains more than 20 unique variants in preclinical development. These include:

- Molecules designed to increase bone mass without the dose-limiting effect on red blood cells observed with wild-type ActRIIA-Fc; and
- Molecules designed to increase muscle and bone mass with reduced BMP9 binding without impacting vascular remodeling that leads to weak blood vessels observed with the wild-type ActRIIB-Fc.

Our discovery approach has built on these initial observations to generate product candidates designed to target ActRII receptors without the liabilities observed in third-party preclinical studies and clinical trials of ActRIIA-Fc and ActRIIB-Fc.

We believe that we are well positioned to advance our product candidates and realize the commercial opportunities in diseases where muscle and bone loss result in a debilitating impact on survival and quality of life, if our product candidates are successfully developed and approved. Our deep knowledge and expertise of the TGF-ß family of proteins provides a streamlined approach to screen and develop novel product candidates for hematological and musculoskeletal diseases.

Manufacturing

We rely, and expect to continue to rely for the foreseeable future, on third-party contract manufacturing organizations, or CMOs, to produce our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. We require that our CMOs produce bulk drug substances and finished drug products in accordance with current Good Manufacturing Practices, or cGMPs, and all other applicable laws and regulations. We maintain agreements with our manufacturers that include confidentiality and intellectual property provisions to protect our proprietary rights related to our product candidates.

We have engaged CMOs to manufacture supply for preclinical and clinical use. Additional CMOs are used to label, package and distribute drug product for preclinical and clinical use. We obtain our supplies from these CMOs on a purchase order basis and do not have any long-term supply arrangements in place. We do not currently have arrangements in place for redundant supply. We are closely monitoring the impact of the COVID-19 pandemic on our ability to procure sufficient supplies for the development of our product candidates. The magnitude of any potential impact will depend on the severity and duration of the spread of the virus, and the actions undertaken to contain COVID-19 or treat its effects. We are working with our CMOs to manage this process. However, we could be unable to find alternative suppliers of acceptable quality, in the appropriate volumes and at an acceptable cost, if needed. As our development programs expand and we build new process efficiencies, we expect to continually evaluate this strategy with the objective of satisfying demand for registration trials and, if approved, the manufacture, sale and distribution of commercial products.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary rights. While we believe that our product candidates, discovery programs, technology, knowledge, experience and scientific resources provide us with competitive

advantages, we compete in the highly competitive markets and face significant competition from many sources, including pharmaceutical and biotechnology companies, as well as academic institutions, governmental agencies and private and public research institutions.

We compete in the segments of the biotechnology, pharmaceutical and other related industries that develop and market therapies for the treatment of hematological and musculoskeletal disorders. There are many other companies, including large biotechnology and pharmaceutical companies, that have commercialized and/or are developing therapies for the same therapeutic areas that our product candidates target. For example, FibroGen Inc., Astellas Pharma Inc. are developing product candidates for the treatment of anemia, and Acceleron Pharma Inc., or Acceleron, Bristol-Myers Squibb Company and Disc Medicine are developing product candidates targeting diseases associated with MDS and myelofibrosis, including chronic anemia. Additionally, in April 2020, Acceleron received FDA approval of its product, Reblozyl, for the treatment of anemia failing an erythropoiesis stimulating agent and requiring two or more red blood cell units over eight weeks in adult patients with very low- to intermediate-risk MDS with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis. In June 2020, Acceleron further announced that the European Commission approved Reblozyl for the treatment of transfusion-dependent anemia in adult patients with MDS or beta thalassemia and in September 2020, Acceleron announced that Health Canada approved Reblozyl for the treatment of adult patients with red blood cell transfusion-dependent anemia associated with beta thalassemia. Sierra Oncology, Inc. is developing momelotinib as a treatment for myelofibrosis. Additionally, Constellation Pharmaceutics, Inc. is also developing a product candidate as a treatment for myelofibrosis.

Other companies that are developing product candidates that are designed to target the TGF-ß signaling pathways include Scholar Rock Holding Corporation, Biogen Inc. and Regeneron Pharmaceuticals, Inc.

There are currently no approved drugs for the treatment of FOP. However, Ipsen, through its subsidiary Clementia Pharmaceuticals Inc. and pursuant to a collaboration with Blueprint Medicines Corporation, as well as Regeneron Pharmaceuticals, Inc., BioCryst Pharmaceuticals, Inc. and Incyte Corporation are developing product candidates for the treatment of FOP that are intended to work, at least in part, through inhibition of aberrant ALK2 signaling.

Many of the companies against which we are competing or against which we may compete in the future, either alone or with their strategic collaborators, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies or universities and research institutions. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and enrolling patients for our clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We could see a reduction or elimination of our commercial opportunity if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. The availability of reimbursement from government and other third-party payors will also significantly affect the pricing and competitiveness of our products. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

Collaborations and License Agreement

2016 Exclusive Patent License Agreement with The General Hospital Corporation

In April 2016, we entered into an exclusive patent license agreement with The General Hospital Corporation, or MGH, which was subsequently amended in May 2017 and February 2018. Under the license agreement with MGH, or the MGH Agreement, we obtained an exclusive, worldwide license, with the right to sublicense, under certain patents and technical information of MGH, to make, have made, use, have used, sell, have sold, lease, have leased, import, have imported or otherwise transfer licensed products and processes for use in the

treatment, diagnosis, palliation and prevention of diseases and disorders in humans and animals. We are required to use commercially reasonable efforts to develop and commercialize licensed products and processes, and must achieve certain required diligence milestones.

Under the terms of the MGH Agreement, we made an initial license payment of $100,000 and reimbursed MGH approximately $280,000 of prior patent prosecution expenses related to the licensed patents. We also issued MGH an aggregate of 358,674 shares of our common stock. Additionally, we are required to pay a low-five digit to mid-five digit annual maintenance fee prior to the first commercial sale of our first product or process, a mid-five digit annual maintenance fee after the first commercial sale of our first product or process that is creditable against royalties, certain clinical and regulatory milestone payments for the first three products or indications to achieve such milestones, which milestone payments are $8.6 million in the aggregate, and certain commercial milestone payments for the first three products or indications to achieve such milestones, which milestone payments are $18.0 million in the aggregate. In 2020, we made a single payment of $50,000 with respect to achievement of the clinical and regulatory milestone of filing of an IND in the first country. We are also obligated to pay tiered royalties on net sales of licensed products ranging in the low-single digits to mid-single digits. The royalty rates are subject to up to a maximum 50% reduction for lack of a valid claim, in the event that it is necessary for us to obtain a license to any third-party intellectual property related to the licensed products, and generic competition. The obligation to pay royalties under the MGH Agreement expires on a licensed product-by-licensed product and country-by-country basis upon the later of expiry of the last valid claim of the licensed patents that cover such licensed product in such country and ten years from the first commercial sale of such product in such country. We are also obligated to pay a percentage of non-royalty related payments received by us from sublicensees ranging in the sub-teen double digits and a change of control fee equal to a low-single digit percentage of the payments received as part of any completed transaction up to a low-seven digit amount.

The MGH Agreement expires upon expiry of the last remaining royalty obligation for a licensed product or process. Under the MGH Agreement, MGH may terminate the agreement upon our uncured material breach or insolvency, a challenge by us of the licensed patents and certain other specified breaches of the MGH Agreement. We may terminate the agreement for any reason upon specified prior written notice to MGH.

Termination of 2017 Research Collaboration and Exclusive License Agreement with Novo Nordisk

In December 2017, we entered into a research collaboration and exclusive license agreement with Novo Nordisk A/S, or Novo Nordisk. Under the agreement with Novo Nordisk, or the Novo Nordisk Agreement, we are collaborating with Novo Nordisk on research and development of fusion molecules consisting of a ligand binder present as part of a larger molecule, or ligand traps. Pursuant to the Novo Nordisk Agreement, Novo Nordisk had the right to select a prespecified number of ligand traps for further development and commercialization by Novo Nordisk. Following execution, Novo Nordisk selected one existing ligand trap to further develop and commercialize and prior to the completion of the two-year research program, selected a second ligand trap arising from the collaboration.

Upon selection by Novo Nordisk of each ligand trap, we transferred the selected ligand trap to Novo Nordisk for further development and commercialization. We are able to further develop and commercialize all other remaining declined ligand traps, subject to certain limitations as described below.

Under the Novo Nordisk Agreement, we granted Novo Nordisk an exclusive, worldwide, royalty bearing license, with the right to sublicense, under certain of our background intellectual property and collaboration intellectual property to develop, manufacture and commercialize products that contain the initial ligand trap and any selected ligand trap, whether alone or as a combination product, for use in the treatment of diabetes (including diabetes related complications of cardiovascular disease, or CVD, and chronic kidney disease, or CKD), obesity, (including obesity related complications of CVD, CKD and sarcopenic obesity), non-alcoholic steatohepatitis and cachexia, and, solely as a combination product for use in CVD and CKD.

Under the terms of the Novo Nordisk Agreement, during the term of the agreement, we are not permitted, directly or indirectly, to research, develop or commercialize any ligand trap or ligand binder for use in the licensed field or any selected ligand trap outside of the licensed field, except that we may research, develop, or commercialize any declined ligand trap for use in CVD and CKD. Under the terms of the Novo Nordisk

Agreement, we received an initial license payment of $16.0 million in 2018. Novo Nordisk has paid us $4.0 million in research funding over the two-year research program.

On October 26, 2020, Novo Nordisk gave written notice of termination of the Novo Nordisk Agreement, effective six months following the delivery of notice, on April 26, 2021. Upon termination, all worldwide rights to all ligand traps selected under the Novo Nordisk Agreement, along with all rights to develop our molecules in the fields of diabetes, obesity, nonalcoholic steatohepatitis and cachexia, will revert to us. Under the terms of the Novo Nordisk Agreement, Novo Nordisk is obligated to continue to reimburse the Company for certain research and development costs through April 26, 2021. Upon effectiveness of the termination, such reimbursements will cease.

Intellectual Property

Overview

We strive to protect the proprietary technology, inventions and improvements that we believe are commercially important to our business, including obtaining, maintaining, enforcing and defending our intellectual property rights, including patent rights, whether developed internally or licensed from third parties. We rely, in part, on trade secrets and know-how relating to our proprietary technology and drug candidates and continuing innovation to develop, strengthen and maintain our proprietary position. We also plan to rely, in part, on data exclusivity, market exclusivity and patent term extensions if and when available. Our commercial success will depend in part on our ability to obtain and maintain patent and other intellectual property protection for our technology, inventions and improvements; to preserve the confidentiality of our trade secrets; to defend and enforce our proprietary rights, including any patents that we own or may obtain in the future; and to operate without infringing, misappropriating or otherwise violating the valid and enforceable patents and other intellectual property rights of third parties. Intellectual property rights may not address all potential threats to our competitive advantage

As of September 30, 2020, our patent portfolio consisted of five issued U.S. patents, 19 pending U.S. patent applications, three issued ex-U.S. patents and 47 pending ex-U.S. applications, with expected expiry dates not earlier than between March 13, 2029 and April 30, 2041. Of these, 52 patent applications relate to KER-050, KER-047 and KER-012, and eight issued patents and 14 patent applications relate to other technologies, in each case as described in more detail below. Each of our pending international patent applications has been filed under the Patent Cooperation Treaty and has not yet entered any national jurisdictions. Our policy is to file patent applications to protect technology, inventions and improvements to inventions that may be commercially important to the development of our business.

We seek U.S. and international patent protection for a variety of technologies, and own patent applications with claims directed to ActRIIA ligand traps, ActRIIB ligand traps, ActRII chimera ligand traps, GDNF fusion polypeptides, ALK2 antibodies, and crystal forms of an ALK2 inhibitor. We also intend to seek patent protection or rely upon trade secret rights to protect other technologies that may be used to discover and validate targets, and that may be used to manufacture and develop novel products. We are a party to license agreements that give us rights to use specific technologies in our products and in manufacturing our products.

Patent applications directed to our most advanced programs are summarized below.

KER-050

KER-050 is a modified ActRIIA ligand trap that is designed to bind to different TGF-ß ligands that signal through a TGF-ß signaling pathway. We own six pending U.S. patent applications and 26 pending ex-U.S. applications that contain claims or supporting disclosure directed to ActRIIA ligand traps and use thereof to treat muscle disease, bone disease, metabolic disease, anemia, fibrosis, pulmonary hypertension, thrombocytopenia, and neutropenia. Any patents issuing from these applications will have expiration dates between November 9, 2037 and March 20, 2041, absent any patent term adjustments or extensions.

KER-047

KER-047 is an orally available small molecule ALK2 inhibitor designed to potently and selectively inhibit ALK2 signaling. We own two pending U.S. patent applications that contain claims or supporting disclosure directed to crystal forms of an ALK2 inhibitor and uses thereof. Any patents issuing from these applications will have

expiration dates between October 25, 2039 and April 30, 2041, absent any patent term adjustments or extensions.

We have exclusively licensed from The General Hospital Corporation rights in one patent family related to novel ALK2 inhibitors. Patents in this family are expected to expire on April 26, 2038, absent any patent term adjustments or extensions.

KER-012

KER-012 is a modified ActRIIB ligand trap that is designed to bind to different TGF-ß ligands that signal through a TGF-ß signaling pathway. We own four pending U.S. patent applications and nine pending ex-U.S. applications that contain claims or supporting disclosure directed to ActRIIB ligand traps and use thereof to treat muscle disease, bone disease, anemia, fibrosis, pulmonary hypertension, metabolic disease, thrombocytopenia, and neutropenia. Any patents issuing from these applications will have expiration dates between January 11, 2039 and March 20, 2041, absent any patent term adjustments or extensions.

Other

We plan to seek United States and international patent protection for a variety of additional technologies. We own six pending U.S. patent applications and eight pending ex-U.S. applications that contain claims or supporting disclosure directed to GDNF fusion polypeptides, ALK2 antibodies, and ActRII chimera ligand traps. Any patents issuing from these applications will have expiration dates between November 9, 2037 and March 20, 2041, absent any patent term adjustments or extensions.

Intellectual Property Protection

Individual patents extend for varying periods depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, patents issued for regularly filed applications in the United States are granted a term of 20 years from the earliest effective non-provisional filing date. In addition, in certain instances, a patent term can be extended to recapture a portion of the U.S. Patent and Trademark Office, or the USPTO, delay in issuing the patent as well as a portion of the term effectively lost as a result of the FDA regulatory review period. However, as to the FDA component, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. The duration of patents outside of the United States varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. However, the actual protection afforded by a patent varies on a product by product basis, from country to country and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

Furthermore, we rely upon trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, employees and consultants and invention assignment agreements with our employees. We also have confidentiality agreements or invention assignment agreements with our collaborators and consultants. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Our commercial success will also depend in part on not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, or our product candidates or processes, obtain licenses or cease certain activities. Our breach of any license agreements or failure to obtain a license to proprietary rights that we may require to develop or commercialize our future product candidates may have an adverse impact on us. If third parties have prepared and filed patent applications prior to March 16, 2013 in the United States that also claim technology to which we have rights, we may have to participate in interference proceedings in the USPTO, to

determine priority of invention. For more information, please see “Risk Factors—Risks Related to Intellectual Property.”

Government Regulation

The FDA and other regulatory authorities at federal, state and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring and post-approval reporting of drug and biological products such as those we are developing.

Our product candidates are subject to regulation under the Food, Drug, and Cosmetic Act and the Public Health Service Act, and other federal, state, local and foreign statutes and regulations. We, along with third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates.

U.S. Drug and Biological Product Regulation

Our product candidates must be approved by the FDA through either a New Drug Application, or NDA, or a Biologics License Application, or BLA. The process required by the FDA before biopharmaceutical product candidates may be marketed in the United States generally involves the following:

- completion of extensive preclinical laboratory tests and animal studies performed in accordance with applicable regulations, including the FDA’s Good Laboratory Practice, or GLP, requirements;
- submission to the FDA of an Investigational New Drug, or IND, application which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, or ethics committee at each clinical site before the trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, good clinical practice, or GCP, requirements and other clinical trial-related regulations to establish the safety and efficacy of the investigational drug product for each proposed indication and to establish the safety, purity and potency of the investigational biologic product candidate for each proposed indication;
- preparation of and submission to the FDA of an NDA for a small molecule product candidate or a BLA for a biologic after completion of all pivotal clinical trials;
- payment of user fees for FDA review of the NDA or BLA;
- a determination by the FDA within 60 days of its receipt of the NDA or BLA to file the application for review;
- satisfactory completion of one or more FDA pre-approval inspections of the manufacturing facility or facilities at which the proposed product will be produced to assess compliance with current Good Manufacturing Practice, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product’s continued identity, strength, quality and purity;
- potential FDA audit of the preclinical study and/or clinical trial sites that generated the data in support of the NDA or BLA;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- FDA review and approval of an NDA or licensure of a BLA, including consideration of the views of any FDA Advisory Committee, prior to any commercial marketing or sale of the product for particular indications for use in the United States; and
- compliance with any post-approval requirements, including the potential requirement to conduct post-approval studies.

Preclinical and Clinical Development

Before testing any drug or biologic candidate in humans in the United States, the product candidate must undergo rigorous preclinical testing. Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as *in vitro* and animal studies to assess safety and in some cases to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal and state regulations and requirements, including GLP regulations for safety/toxicology studies.

Prior to beginning the first clinical trial with a product candidate, we must submit the results of the preclinical studies, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of an IND. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The IND submission contains the general investigational plan and the protocol or protocols for preclinical studies and clinical trials, as well as results of in vitro and animal studies assessing the toxicology, pharmacokinetics, pharmacology and pharmacodynamic characteristics of the product, chemistry, manufacturing and controls information, and any available human data or literature to support the use of the investigational product. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day period, raises safety concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

The clinical stage of development involves the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. These investigators are generally physicians who are not employed by or under the trial sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used in monitoring subject safety and assessing efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the existing IND. Furthermore, each clinical trial must be reviewed and approved by an independent IRB for each institution at which the clinical trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative, and must monitor the study until completed. Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing preclinical studies and clinical trials and clinical study results to public registries.

A sponsor who wishes to conduct a clinical trial outside of the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA. The FDA will accept a well-designed and well-conducted foreign clinical trial not conducted under an IND if the trial was conducted in accordance with GCP requirements and the FDA is able to validate the data through an onsite inspection, if deemed necessary, and the practice of medicine in the foreign country is consistent with the United States.

Human clinical trials in the United States are typically conducted in three sequential phases that may overlap or be combined:

- Phase 1 clinical trials generally involve a small number of healthy volunteers or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.
- Phase 2 clinical trials involve studies in a limited population of disease-affected patients to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks.
- Phase 3 clinical trials generally involve a large number of patients at multiple geographically dispersed clinical trial sites and are designed to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.

When these phases overlap or are combined, the trials may be referred to as Phase 1/2 or Phase 2/3. A Phase 1/2 clinical trial is a human trial that investigates both safety and preliminary efficacy of an investigational therapy. A Phase 2/3 clinical trial is a human trial that investigates both preliminary and confirmatory efficacy and safety to potentially support submission of a marketing application with the applicable regulatory authorities.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies, are used to gain additional experience from the treatment of patients in the intended therapeutic indication and are commonly intended to generate additional safety data regarding use of the product in a clinical setting. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition to FDA approval of an NDA or BLA.

Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the chemistry and physical characteristics of the product candidate, and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. The FDA or the sponsor or its data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product candidate has been associated with unexpected serious harm to patients. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Sponsors of clinical trials of FDA-regulated products, including biologics, are required to register and disclose certain clinical trial information, which is publicly available at www.clinicaltrials.gov.

FDA Review Process

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA. The NDA or BLA is a request for approval to market the drug or biologic for one or more specified indications and must contain proof of safety and efficacy for a drug or safety, purity and potency for a biologic. The application must include all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results of preclinical studies and clinical trials, as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product's use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational product to the satisfaction of FDA.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each submission of an NDA or BLA requires payment of a substantial application user fee to the FDA, unless a waiver or exemption applies. The FDA adjusts the PDUFA user fees on an annual basis. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs or BLAs for products designated as orphan drugs, unless the product application also includes a non-orphan indication.

The FDA reviews all submitted NDAs and BLAs before it accepts them for filing, and may request additional information rather than accepting the NDA or BLA for filing. The FDA must make a decision on accepting an NDA or BLA for filing within sixty days of receipt. Such decision could include either issue a refusal to file letter or acceptance of the NDA or BLA for filing, indicating that it is sufficiently complete to permit substantive review.

Once an NDA or BLA has been accepted for filing, the FDA begins an in-depth review of the NDA or BLA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA aims to review standard applications within ten months from the filing date, during which it will complete its initial review of a new molecular entity NDA or original BLA and respond to the applicant, or within six months from the filing date of a new molecular entity NDA or original BLA designated for priority review. In both standard and priority reviews, the FDA does not always meet its PDUFA goal dates, and the review process is often significantly extended by FDA requests for additional information or clarification. The FDA reviews the application to determine, among other things, whether a product is safe and effective, or for a biologic, safe, pure and potent for its intended use, and whether the facility in which it is manufactured, processed, packed or held meets standards designed to assure and preserve the product's identity, safety, strength, quality, potency and purity.

The FDA generally accepts data from foreign clinical trials in support of an NDA or BLA if the trials were conducted under an IND, and the IND requirements, unless waived, were met. If a foreign clinical trial is not conducted under an IND, the FDA nevertheless may accept the data in support of an NDA or BLA if the trial was conducted in accordance with GCPs and the FDA is able to validate the data through an on-site inspection, if deemed necessary. Although the FDA generally requests that marketing applications be supported by some data from domestic clinical studies, the FDA may accept foreign data as the sole basis for marketing approval if (1) the foreign data are applicable to the U.S. population and U.S. medical practice, (2) the trials were performed by clinical investigators with recognized competence, and (3) the data may be considered valid without the need for an on-site inspection or, if the FDA considers the inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means.

Before approving an NDA or BLA, the FDA will conduct a pre-approval inspection of the manufacturing facility or facilities for the new product to determine whether they comply with cGMP requirements. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA also may audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel products or products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions, if any. The FDA is not bound by recommendations of the advisory committee, but it considers such recommendations when making decisions on approval. Additionally, before approving an NDA or BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates an NDA or BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be manufactured, the FDA will issue an approval letter or a Complete Response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response letter usually describes all of the specific deficiencies that the FDA has identified in the NDA or BLA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response letter without first conducting required inspections, testing submitted product lots and/or reviewing proposed labeling. In issuing the Complete Response letter, the FDA may recommend actions that the applicant might take to place the application in condition for approval, including requests for additional information or clarification, which may include the potential requirement for additional clinical studies, including the potential requirement to conduct additional clinical trial(s) and/or to complete other significant and time-consuming requirements related to clinical trials, or to conduct additional preclinical studies or manufacturing activities. If a Complete Response Letter is issued, the applicant may either resubmit the NDA or BLA, addressing all of the deficiencies identified in the letter, or withdraw the application or request an opportunity for a hearing. Even if such data and information are submitted, the FDA may decide that the NDA or BLA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States for which there is no reasonable expectation that the cost of developing and making available in the United States a drug or biologic for this type of disease or condition will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. The orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review or approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full NDA or BLA, to market the same product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the application fee.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Post-Approval Requirements

Following approval of a new product, the manufacturer and the approved product are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to monitoring and record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, compliance with advertising and promotion requirements, which include restrictions on promoting the product for unapproved uses or patient populations, known as “off-label use,” and limitations on industry-sponsored scientific and educational activities. Further, after approval, if there are any changes or modifications to the approved product, including changes in indications, labeling or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA review and approval of a new NDA/BLA or NDA/BLA supplement, which may require the development of additional data or preclinical studies and clinical trials.

The FDA may also place other conditions on approvals including the requirement for a Risk Evaluation and Mitigation Strategy, or REMS, to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the NDA or BLA must submit a proposed REMS. A REMS is a safety strategy to manage a known or potential serious risk associated with a product and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA will not approve the NDA or BLA without an approved REMS, if required. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product’s safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies. Product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or

failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning or untitled letters or holds on post-approval clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;
- product seizure or detention, or refusal of the FDA to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- mandated modification of promotional materials and labeling and the issuance of corrective information;
- the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or
- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of drugs and biologics. Drugs and biologics may be promoted only for the approved indications and in accordance with the provisions of the approved label. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. To date, only a handful of biosimilars have been licensed under the BPCIA, although numerous biosimilars have been approved in Europe. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing

the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

A biological product can also obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety, and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable foreign regulatory authorities before we can commence clinical trials or marketing of the product in foreign countries and jurisdictions.

Australia

Our Phase 1 trial for KER-047 and our Phase 1 trial for KER-050 were both conducted in Australia, and our Phase 2 trial for KER-050 is being conducted in Australia. The Therapeutic Goods Administration, or the TGA, and the National Health and Medical Research Council set the GCP requirements for clinical research in Australia, and compliance with these codes is mandatory. Australia has also adopted international codes, such as those promulgated by the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, or the ICH. The ICH guidelines must be complied with across all fields of clinical research, including those related to pharmaceutical quality, nonclinical and clinical data requirements and trial designs. The basic requirements for preclinical data to support a first-in-human trial under ICH guidelines are applicable in Australia. Requirements related to adverse event reporting in Australia are similar to those required in other major jurisdictions.

Clinical trials conducted using "unapproved therapeutic goods" in Australia, being those which have not yet been evaluated by the TGA for quality, safety and efficacy must occur pursuant to either the Clinical Trial Notification Scheme, or the CTN Scheme, or the Clinical Trial Exemption Scheme, or the CTX Scheme. In each case, the trial is supervised by a Human Research Ethics Committee, or HREC, an independent review committee set up under guidelines of the Australian National Health and Medical Research Council that ensures the protection of rights, safety and well-being of human subjects involved in a clinical trial. A HREC does this by reviewing, approving and providing continuing examination of trial protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The CTN Scheme broadly involves:

- completion of preclinical laboratory and animal testing;
- submission to a HREC, of all material relating to the proposed clinical trial, including the trial protocol;
- the institution or organisation at which the trial will be conducted, referred to as the "Approving Authority", giving final approval for the conduct of the trial at the site, having regard to the advice from the HREC; and
- the investigator submitting a 'Notification of Intent to Conduct a Clinical Trial' form, or CTN Form, to the TGA. The CTN form must be signed by the sponsor, the principal investigator, the chairman of the HREC and a person responsible from the Approving Authority. The TGA does not review any data relating to the clinical trial however CTN trials cannot commence until the trial has been notified to the TGA.

Under the CTX Scheme:

- a sponsor submits an application to conduct a clinical trial to the TGA for evaluation and comment; and

- a sponsor must forward any comments made by the TGA Delegate to the HREC(s) at the sites where the trial will be conducted.

A sponsor cannot commence a trial under the CTX Scheme until written advice has been received from the TGA regarding the application and approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted.

Approval for inclusion in the Australian Register of Therapeutic Goods, or ARTG, is required before a pharmaceutical product may be marketed (or imported, exported or manufactured) in Australia. In order to obtain registration of the product on the ARTG, it is required that:

- adequate and well-controlled clinical trials demonstrate the quality, safety and efficacy of the therapeutic product;
- evidence is compiled which demonstrates that the manufacture of the therapeutic product complies with the principles of cGMP;
- manufacturing and clinical data is derived to submit to the Advisory Committee on Prescription Medicines, which makes recommendations to the TGA as to whether or not to grant approval to include the therapeutic product in the ARTG; and
- an ultimate decision is made by the TGA whether to include the therapeutic product in the ARTG.

Other Healthcare Laws and Compliance Requirements

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such laws include, without limitation: the U.S. federal Anti-Kickback Statute, the civil False Claims Act, U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, and similar foreign, federal and state fraud and abuse, transparency and privacy laws.

The U.S. federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, to induce, or in return for, either the referral of an individual, or the purchase or recommendation of an item or service for which payment may be made under any federal healthcare program. The term remuneration has been interpreted broadly to include anything of value, including stock options. The U.S. federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and others on the other hand. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, but they are drawn narrowly, and practices that involve remuneration, such as consulting agreements, that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the U.S. federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Our practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, a claim including items or services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act.

Civil and criminal false claims laws, including the civil False Claims Act, which can be enforced through civil whistleblower or *qui tam* actions, and civil monetary penalty laws prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment to the federal government, including federal healthcare programs, that are false or fraudulent. For example, the civil False Claims Act prohibits any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes “any request or demand” for money or property presented to the U.S. government. Pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product.

HIPAA created additional federal civil and criminal liability for, among other things, executing a scheme to defraud any healthcare benefit program, including private third-party payors, and making false statements relating to healthcare matters. Similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, HIPAA, as amended by HITECH, and their implementing regulations, impose certain requirements on HIPAA covered entities, which include certain healthcare providers, healthcare clearing houses and health plans, and individuals and entities that provide services on their behalf that involve individually identifiable health information, known as business associates, as well as their covered subcontractors, relating to the privacy, security and transmission of individually identifiable health information.

The U.S. federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to certain payments and other transfers of value made in the prior year to physicians, as defined under such law, and teaching hospitals, as well as ownership and investment interests held by such physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding their relationships with physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and certified nurse midwives during the previous year.

We are also subject to additional similar U.S. state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, or that apply regardless of payor, state laws which require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, state and local laws which require pharmaceutical companies to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, state laws which require the reporting of information related to drug pricing, state and local laws requiring the registration of pharmaceutical sales representatives, and state and foreign laws governing the privacy and security of health information which, in some cases, differ from each other in significant ways, and may not have the same effect, thus complicating compliance efforts. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply, we may be subject to penalties, including, without limitation, significant civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid or similar programs in other countries or jurisdictions, integrity oversight and reporting obligations to resolve allegations of non-compliance, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any pharmaceutical or biological product for which we obtain regulatory approval. Sales of any product, if approved, depend, in part, on the extent to which such product will be covered by third-party payors, such as federal, state, and foreign government healthcare programs, commercial insurance and managed healthcare organizations, and the level of reimbursement, if any, for such product by third-party payors. No uniform policy for coverage and reimbursement exists in the United States, and coverage and reimbursement can differ significantly from payor to payor. Decisions regarding whether to cover any of our product candidates, if approved, the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicare determinations. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization. In addition, companion diagnostic tests

require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical or biological products, will apply to companion diagnostics.

In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical or biological products, medical devices and medical services, in addition to questioning safety and efficacy. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product that receives approval. Decreases in third-party reimbursement for any product or a decision by a third party not to cover a product could reduce physician usage and patient demand for the product. No regulatory authority has granted approval for a personalized cancer immunotherapy based on a vaccine approach, and there is no model for reimbursement of this type of product.

Healthcare Reform

The United States 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 United States, 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.

The ACA, which was enacted in March 2010, substantially changed the way healthcare is financed by both governmental and private insurers in the United States, and significantly affected the pharmaceutical industry. The ACA contains a number of provisions of particular import to the pharmaceutical and biotechnology industries, including, but not limited to, those governing enrollment in federal healthcare programs, a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, and annual fees based on pharmaceutical companies' share of sales to federal healthcare programs. Since its enactment, there have been judicial, Congressional and executive branch challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing penalties, which started on January 1, 2019, for not complying with ACA's individual mandate to carry health insurance, delaying the implementation of certain ACA-mandated fees, and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. On December 14, 2018, a U.S. District Court Judge in Texas ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of legislation enacted in 2017, informally titled the Tax Cuts and Jobs Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit ruled that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case.

Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year and reduced payments to several types of Medicare providers. These reductions went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through December 31, 2020, unless additional action is taken by Congress.

Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several 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 drug products. At the federal level, the Trump administration's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses and place limits on pharmaceutical price increases. Further, the Trump administration previously released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contained proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The Department of Health and Human Services, or HHS, has solicited feedback on certain of these measures and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. On July 24, 2020, the Trump administration announced four executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals, including a policy that would tie certain Medicare Part B drug prices to international drug prices, the details of which were released on September 13, 2020 and expanded the policy to cover certain Part D drugs; one that directs HHS to finalize the Canadian drug importation proposed rule previously issued by HHS and makes other changes allowing for personal importation of drugs from Canada; one that directs HHS to finalize the rulemaking process on modifying the anti-kickback law safe harbors for discounts for plans, pharmacies, and pharmaceutical benefit managers; and one that reduces costs of insulin and epipens to patients of federally qualified health centers. The FDA also recently released a final rule, effective November 30, 2020, implementing a portion of the importation executive order providing guidance for states to build and submit importation plans for drugs from Canada. Although a number of these and other measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic. For example, on August 6, 2020, the Trump administration issued another executive order that instructs the federal government to develop a list of "essential" medicines and then buy them and other medical supplies from U.S. manufacturers instead of from companies around the world, including China. The order is meant to reduce regulatory barriers to domestic pharmaceutical manufacturing and catalyze manufacturing technologies needed to keep drug prices low and the production of drug products in the United States.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern the use, handling and disposal of various biologic, chemical and radioactive substances used in, and wastes generated by, operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. Equivalent laws have been adopted in other countries that impose similar obligations.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits U.S. corporations and individuals from engaging in certain activities to obtain or retain business abroad or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The scope of the FCPA includes interactions with

certain healthcare professionals in many countries. Equivalent laws have been adopted in other foreign countries that impose similar obligations.

Employees and Human Capital Resources

As of September 30, 2020, we had 32 full-time employees, including ten who hold Ph.D. or M.D. degrees. Of these full-time employees, 22 employees are engaged in research and development and ten employees are engaged in management or general and administrative activities. None of our employees are subject to a collective bargaining agreement or represented by a trade or labor union. We consider our relationship with our employees to be good.

Our human capital objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards and cash-based performance bonus awards.

Facilities

Our principal office is located at 99 Hayden Avenue, Suite 120, Building E, Lexington, Massachusetts 02421, where we lease approximately 10,400 square feet of office and laboratory space under a lease that terminates in 2022. We believe that these facilities will be adequate for our near-term needs. If required, we believe that suitable additional or substitute space will be available in the future on commercially reasonable terms to accommodate any such expansion of our operations.