

**KEROS**  
THERAPEUTICS

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## **Corporate Presentation**

January 2021

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# Harnessing the Powerful Biology of the TGF- $\beta$ Superfamily

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- Clinical-stage biopharmaceutical company developing novel therapeutics that target the TGF- $\beta$  superfamily
- Approach validated by marketed products, Infuse (BMP2) for spinal fusion and Reblozyl® (modified activin receptor IIB) for treatment of anemia in  $\beta$ -thalassemia and myelodysplastic syndromes
- Leveraging our extensive experience in TGF- $\beta$  superfamily protein structure, function and protein engineering to generate a clinical pipeline of differentiated therapeutics:

## **KER-050:** Modified activin receptor IIA (ActRIIA) ligand trap

- Designed to address ineffective hematopoiesis by modulating TGF- $\beta$  superfamily signaling
- Potential to correct multiple cytopenias in patients with MDS and myelofibrosis (MF)

## **KER-047:** Activin receptor-like kinase-2 (ALK2) inhibitor being developed for the treatment of anemia resulting from iron imbalance, including iron deficiency anemia (IDA) and iron-refractory iron deficiency anemia (IRIDA), as well as fibrodysplasia ossificans progressiva (FOP)

- Expect to initiate two Phase 2 trials in 2021 – one in patients with IDA and one in patients with IRIDA
- Potential to treat anemia associated with chronic inflammation

## **KER-012:** Proprietary selective activin receptor ligand trap in preclinical development for the treatment of disorders associated with bone loss and pulmonary arterial hypertension (PAH)



# Keros is Developing Differentiated Clinical Assets in Hematological and Musculoskeletal Disorders

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
	KER-047 (small molecule)	Iron deficiency anemia				Completed expanded Phase 1 clinical trial	Initiate Phase 2 trials in IDA and IRIDA: 2021
		Anemia from high hepcidin					
Musculoskeletal		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.





# KER-050

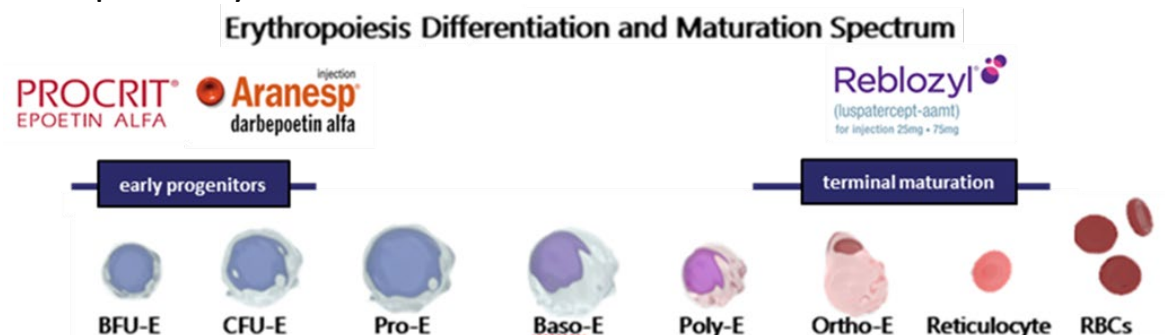
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A novel treatment designed to address diseases arising from ineffective hematopoiesis

- Myelodysplastic syndromes
- Myelofibrosis

# Myelodysplastic Syndromes (MDS) Overview

- Hematologic malignancy predominantly affecting the elderly, resulting in multiple cytopenias (anemia, thrombocytopenia, neutropenia) due to ineffective hematopoiesis
  - 60,000-170,000 MDS patients in U.S.\*
  - 15,000-20,000 newly diagnosed MDS patients in U.S. each year\*
- 90% of patients are anemic and 40-65% have thrombocytopenia
- Platelet transfusion for thrombocytopenia
- Anemia treatments include red blood cell (RBC) transfusions, erythropoiesis-stimulating agents (ESAs) and Reblozyl®
  - ESAs only impact early progenitors in red blood cell lineage and benefit is limited to patients with low transfusion burden and low endogenous EPO levels
  - Reblozyl® approved for treatment of anemia in RS positive patients
  - Approximately 15% of all MDS patients are RS positive and have defects in terminal maturation
    - 38% responders vs 13% placebo
    - Similar to ESAs, benefit primarily in low transfusion burden





# KER-050 is a Modified ActRII Fusion Protein

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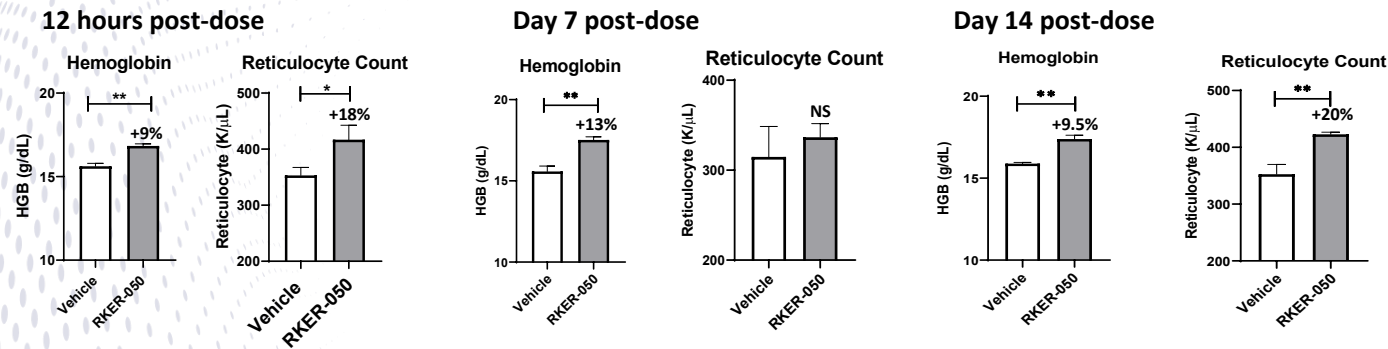
- Activin receptors are expressed on hematopoietic cells and modulate differentiation of precursor cells
- KER-050 is a ligand trap composed of a modified extracellular domain of activin receptor IIA (ActRIIA) fused to the Fc region of human IgG
- KER-050 is designed to increase RBC and platelet production by inhibiting the signaling of ligands through activin receptors
- Preclinical data demonstrate that increased RBCs by potentially increasing differentiation through multiple stages of erythropoiesis
  - Observed increases in platelets also potentially supports action throughout the thrombopoiesis pathway
- Phase 1 clinical trial of KER-050 recapitulated preclinical data with observed rapid, sustained and dose-dependent increases in RBCs and platelets



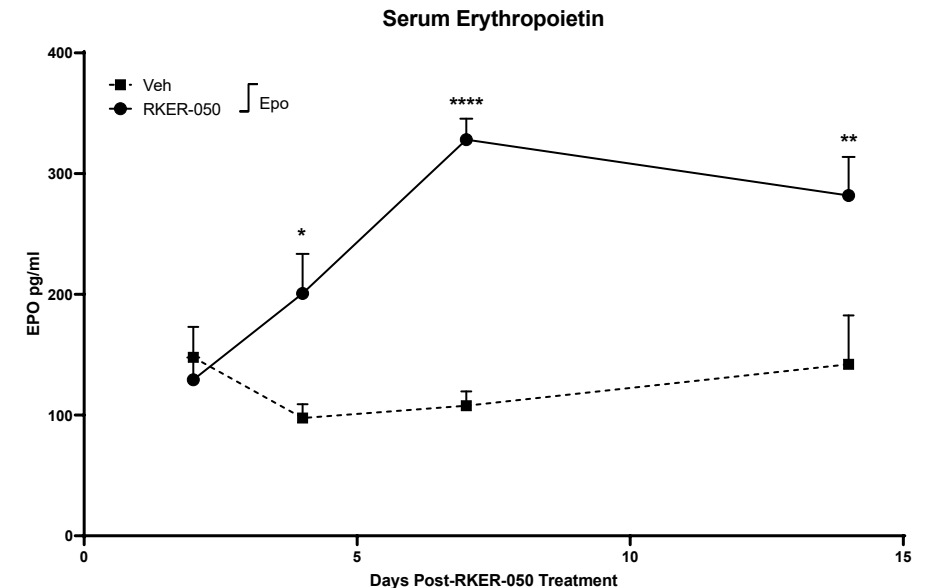
# Treatment with RKER-50 Increased Erythropoiesis by Potentially Promoting Maturation at Multiple Stages and Increased Serum Erythropoietin

- In a preclinical study conducted in mice, a single, subcutaneous 10 mg/kg dose of a mouse version of KER-050 (RKER-050) resulted in:
  - Rapid increase in RBCs
  - Sustained increase continuing to at least 14 days post-dose
  - 2-3-fold increase in circulating erythropoietin
- KER-050 potentially acts on multiple stages across the RBC differentiation spectrum, including common myeloid cells

## Increase in Red Blood Cells and Reticulocytes in Mice



## Observed Increase in Serum Erythropoietin in Mice



\* P value  $\leq 0.05$ ; \*\* P value  $\leq 0.01$ ; \*\*\*\* P value  $\leq 0.0001$





# KER-050 Completed First-in-human Trial

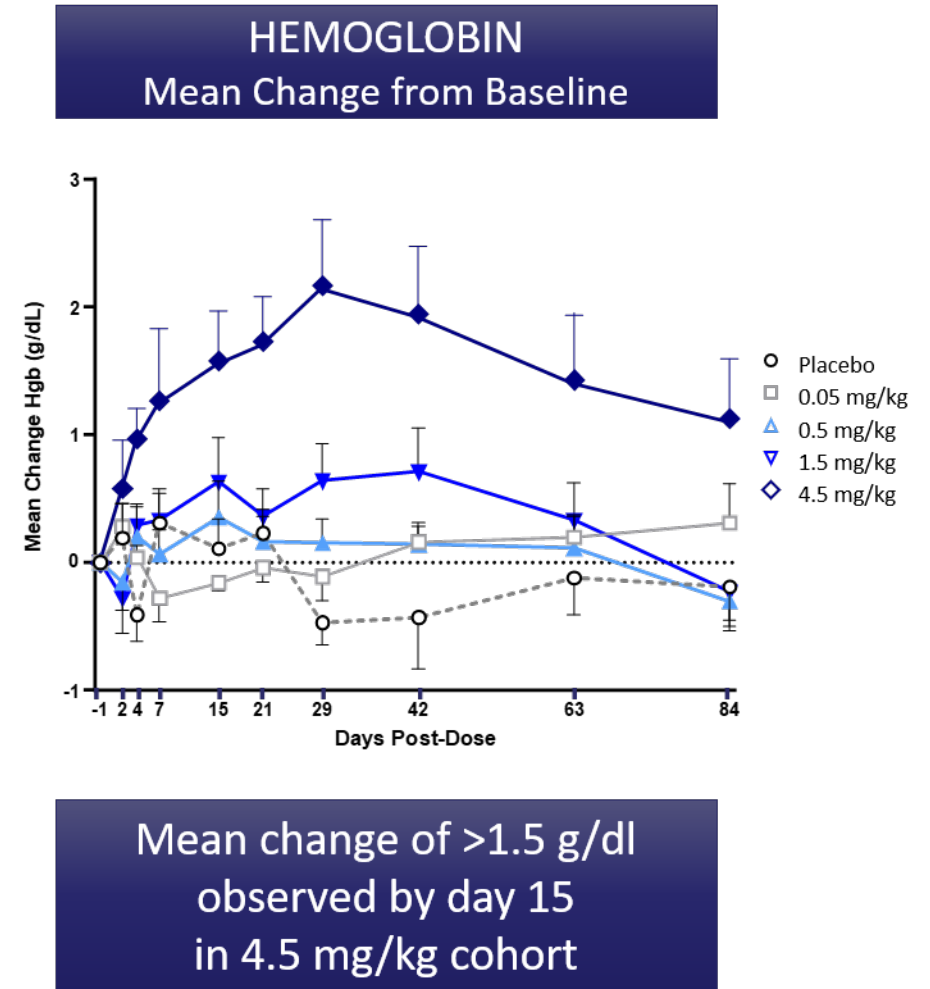
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- First-in-human trial was designed to explore the safety, tolerability and PK in healthy volunteers with a secondary objective to evaluate changes in PD (hematology and bone biomarkers)
- Observed that KER-050 drug levels were dose proportional in Part 1 of the KER-050 Phase 1 clinical trial, with a mean half-life of approximately 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
- Observed to be well tolerated at dose levels up to 4.5 mg/kg, the highest dose level tested
- Notable adverse event:
  - Reversible, mild hypertension events observed only in subjects with an approximately 3 g/dL increase in hemoglobin



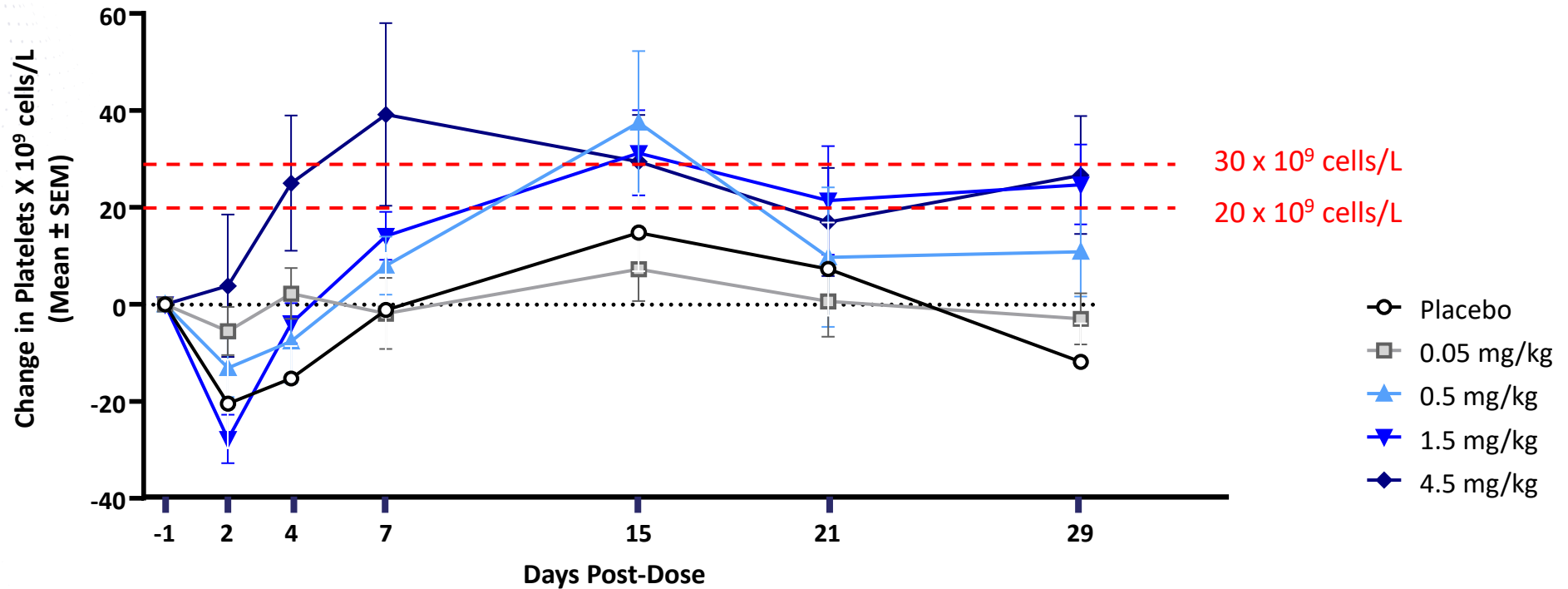
# KER-050 Phase 1 Clinical Trial Recapitulated Learnings from Preclinical Studies

- Single, subcutaneous administration of KER-050 in healthy volunteers
- Observed rapid increase in red blood cell parameters is supportive of acceleration of maturation of late-stage precursors
  - Reticulocytes, red blood cells and hemoglobin
- Observed sustained increase from single dose supports monthly or less frequent dosing
  - Increases in RBC observed through day 29 are supportive of KER-050 acting on multiple stages of erythropoiesis
  - Maximum drug levels were observed on day 4



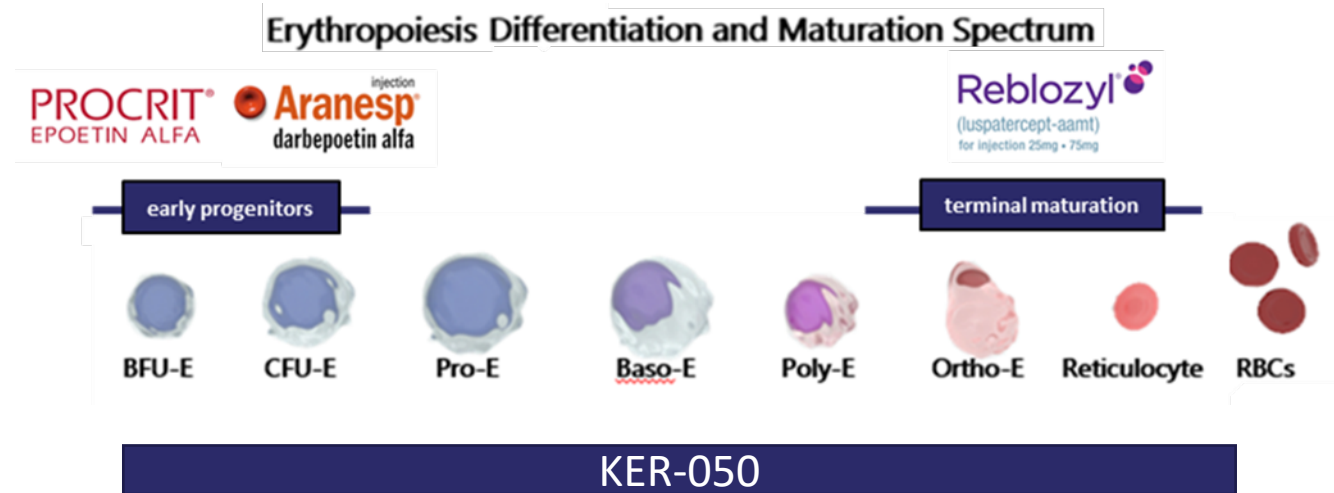
# KER-050 Treatment was Observed to Lead to Clinically Meaningful Changes in Platelets after a Single Dose

Mean Change from Baseline in Platelets at Each Dose



# KER-050 has a Potentially Differentiated Mechanism of Action

- Robust and sustained increases observed in RBCs, hemoglobin and reticulocytes support the potential for administration of monthly or less frequent dosing
- Observed sustained response potentially supports the dual mechanism of promoting early and late stages of erythropoiesis

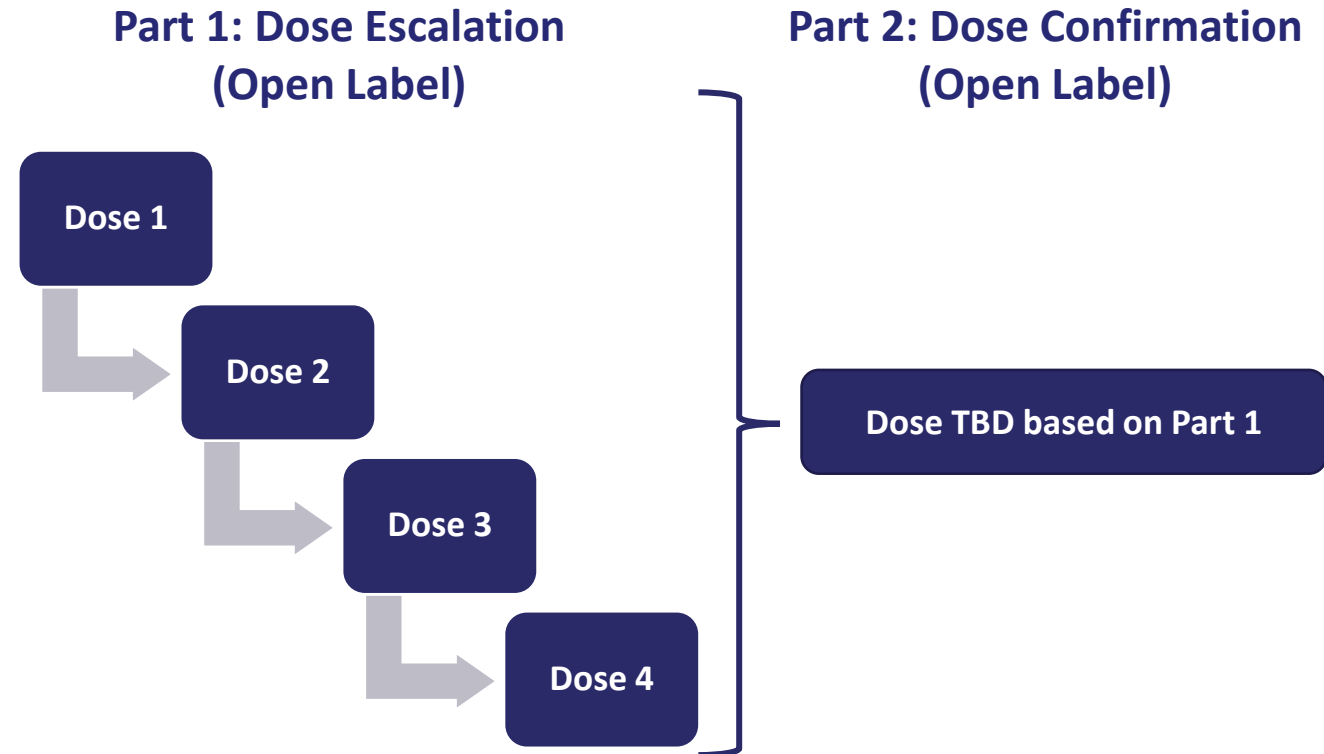


- Clinically meaningful increase observed in platelets after a single dose, which we believe differentiates KER-050 from other agents that only affect RBCs



# Initiated a Phase 2 Trial of KER-050 in MDS

- Open label Phase 2 trial in two parts to explore changes in hematology with treatment in patients with MDS
  - Red blood cell parameters
  - Platelets
- 12-week treatment with monthly dosing and 12-week follow up
- Part 1: Dose escalation to evaluate response in RS positive and non-RS patients
- Part 2: Dose confirmation



Treatment in Parts 1 and 2: 12 weeks  
Safety follow up: 12 weeks



# Myelofibrosis (MF) is Characterized by Ineffective Hematopoiesis

- Molecular abnormalities in JAK-STAT pathway result in expansion of RBC and platelet precursors and subsequent ineffective hematopoiesis
- Megakaryocyte accumulation/breakdown is implicated in the inducement of bone marrow fibrosis
- KER-050 increased RBCs and platelets in our Phase 1 clinical trial
- Plan to initiate a Phase 2 trial in MF in 2021, evaluating effect on platelets and RBCs
  - We believe that KER-050 has the potential to address ineffective hematopoiesis, which is central to MF

**16,000-18,500**

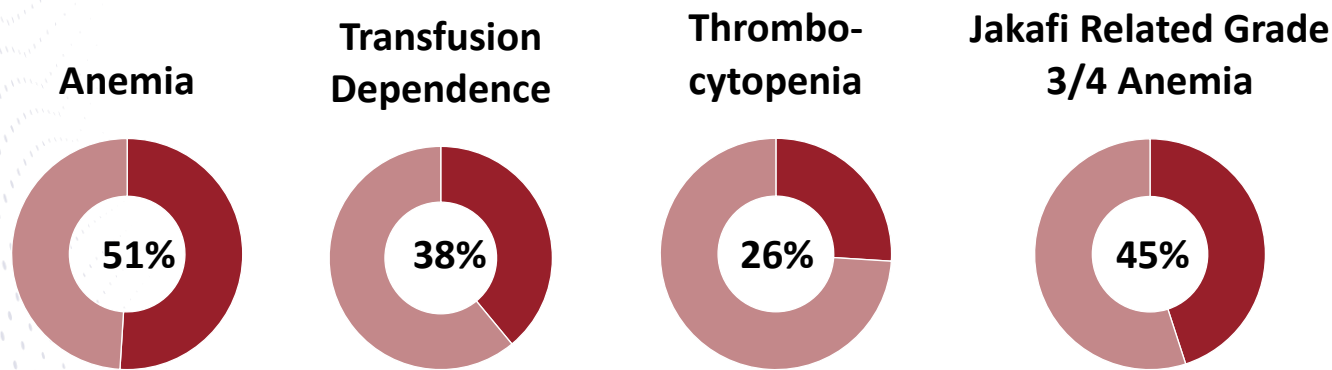
Prevalence of MF patients in US\*

**>3,000**

New MF patients diagnosed each year\*\*

**~100 %**

Nearly all MF patients will become transfusion-dependent\*\*\*



Within 1 year of diagnosis

\*Gangat 2011; \*\*Srouer 2016; \*\*\*Naymagon 2017







# KER-047

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A novel treatment designed to address:

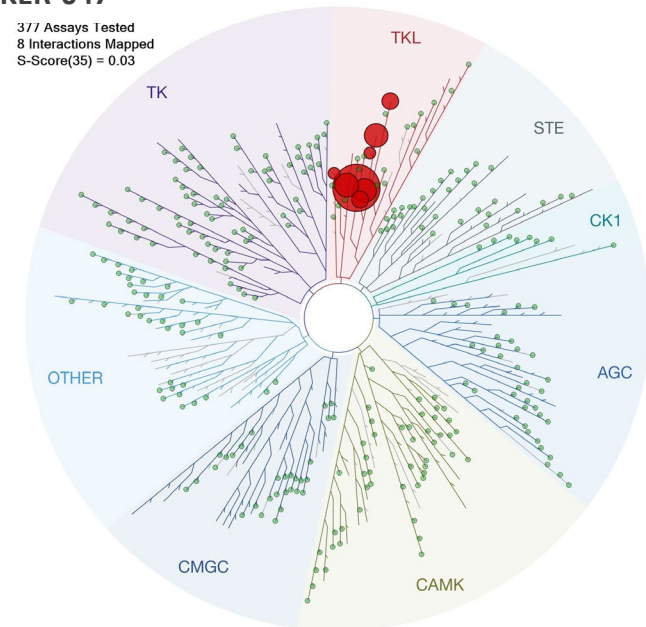
- Anemia resulting from iron imbalance
  - Iron deficiency anemia
  - IRIDA
- Fibrodysplasia ossificans progressiva (FOP)

# KER-047: A Potentially Potent and Selective ALK2 Inhibitor

- **Small molecule inhibitor of the activin receptor-like kinase-2 (ALK2) kinase domain**
- **Potency:** Low nanomolar  $IC_{50}$
- **Selectivity:** Highly selective over kinases outside of the TGF- $\beta$  superfamily as well as other, structurally similar TGF- $\beta$  receptors
  - Data from cell-based reporter assays established > 20-fold potency for ALK2 compared to ALK1 and ALK5, which have 77% and 65% homology to ALK2, respectively (Kingsley, D.M., 1994)
- **PK/ADME:** Suitable for 1x daily oral dosing

KER-047

377 Assays Tested  
8 Interactions Mapped  
S-Score(35) = 0.03

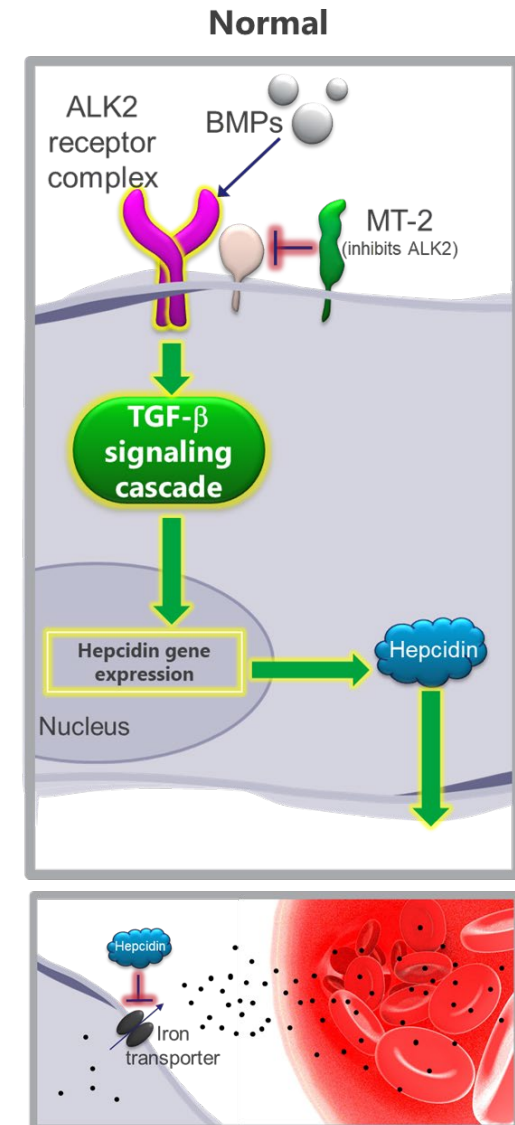


In vitro kinase screen at 1  $\mu$ M



# ALK2 Regulates Hepcidin and Iron Homeostasis

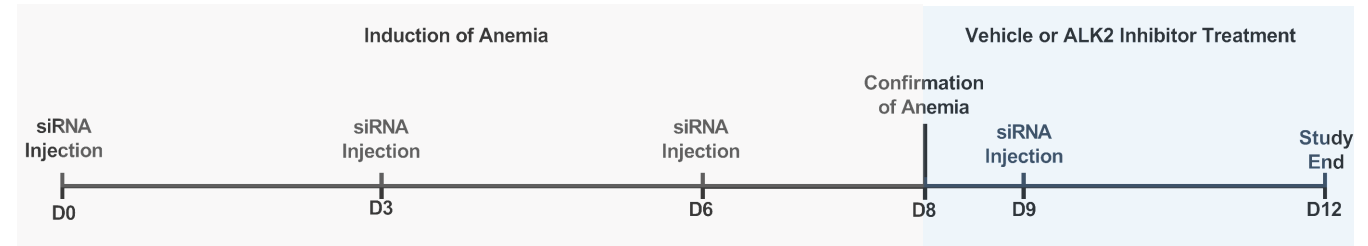
- ALK2 signaling in the liver controls hepcidin expression, a hormone that controls iron homeostasis
- Excessive ALK2 signaling results in high hepcidin and a shortage of iron availability for RBC production
- ALK2 signaling requires BMP ligand and the co-receptor hemojuvelin
- Hepcidin expression is tightly regulated and controls expression of the ALK2 suppressor protease MT-2
  - The genetic disease iron-refractory iron deficiency anemia (IRIDA) is characterized by loss of MT-2
- High hepcidin has also been implicated in anemia of chronic disease
- Modulating ALK2 signaling will normalize high hepcidin levels, restore serum iron and ameliorate anemia



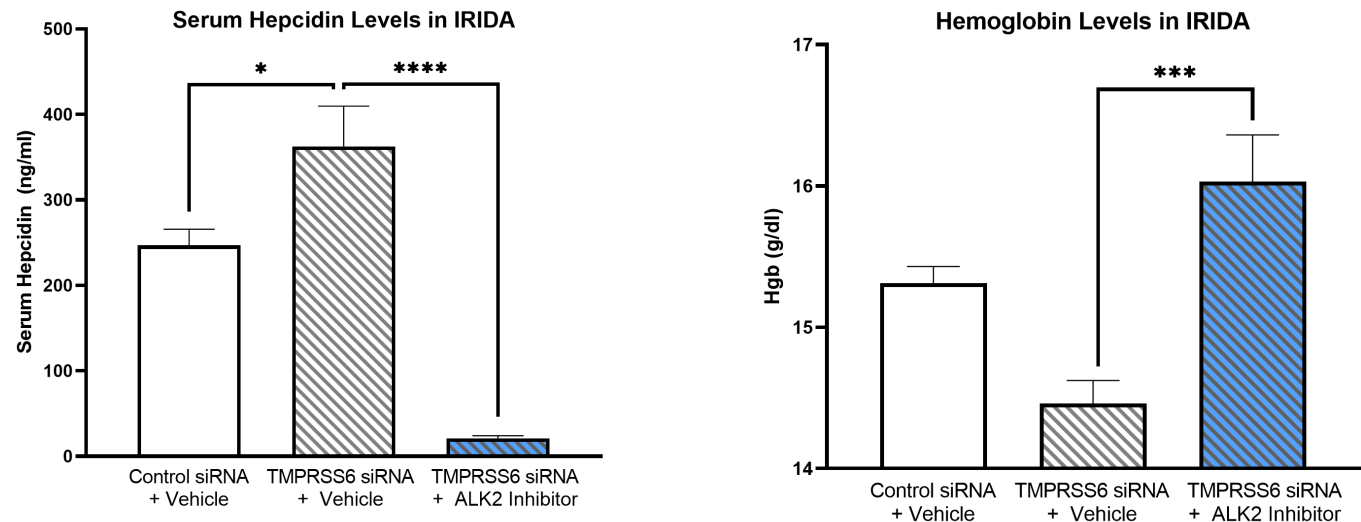
# Keros ALK2 Inhibitors Shown to Resolve Anemia in the Mouse Model of IRIDA

- TMPRSS6 encodes MT-2, the protease that suppresses ALK2 signaling
- MT-2/TMPRSS6 deficiency results in IRIDA
- siRNA knockdown of TMPRSS6 in mice mimics changes seen in human IRIDA patients
  - Increases hepcidin and reduces hemoglobin
- Our small molecule ALK2 inhibitor reversed high hepcidin and ameliorated anemia resulting from TMPRSS6 deficiency in wild-type mice

## Mouse IRIDA Model Protocol Timeline



## Mouse IRIDA Model Data



\*P>0.05; \*\*\*P>0.001; \*\*\*\*P>0.0001 (Two-way ANOVA followed by Sidak post test)



# KER-047: Expanded Phase 1 Clinical Trial Recapitulated the Observations from Preclinical Studies

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- All single ascending and multiple ascending dose cohorts evaluated (including additional cohort) (“expanded trial”)
- The objective of the Phase 1 clinical trial was to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamic effects of single and multiple ascending dose levels of KER-047 in healthy volunteers
  - In the multiple ascending dose cohorts, KER-047 was administered as daily doses of 50-350 mg for approximately 7 days
- Multiple pharmacodynamic biomarkers were included to assess KER-047’s inhibition of ALK2
  - Reduction in hepcidin was observed at each dose level tested in Part 2 of the expanded trial
  - Observed rapid and dose-related increases in serum iron and transferrin saturation in the expanded trial
  - We believe iron mobilization led to increased iron bioavailability for incorporation into reticulocyte hemoglobin. 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 the expanded trial
- Reductions in total cholesterol, low-density lipoproteins (LDL) and high-density lipoproteins were observed in Part 2 of the 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.
- There were no serious adverse events reported in either part of this expanded trial
- Most common adverse events observed: abdominal discomfort, chills, decreased appetite, diarrhea, dizziness, fatigue, gastroenteritis, headache, lymphopenia, myalgia, nausea, neutropenia, pyrexia, rhinorrhea, tonsilitis, upper abdominal pain and vomiting



# Phase 2 Trials to Provide Proof-of-Concept for Treatment of Anemia Resulting from Iron Imbalance, Including IDA and IRIDA

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## Iron Deficiency Anemia

- KER-047 is designed to re-establish normal iron homeostasis by mobilizing iron out of tissues, thereby ameliorating anemia
- We expect to initiate a Phase 2 clinical trial in patients with iron deficiency anemia in 2021

## IRIDA

- KER-047 is designed to normalize high hepcidin levels, restore serum iron and ameliorate anemia
- We expect to initiate a Phase 2 clinical trial in patients with IRIDA in 2021

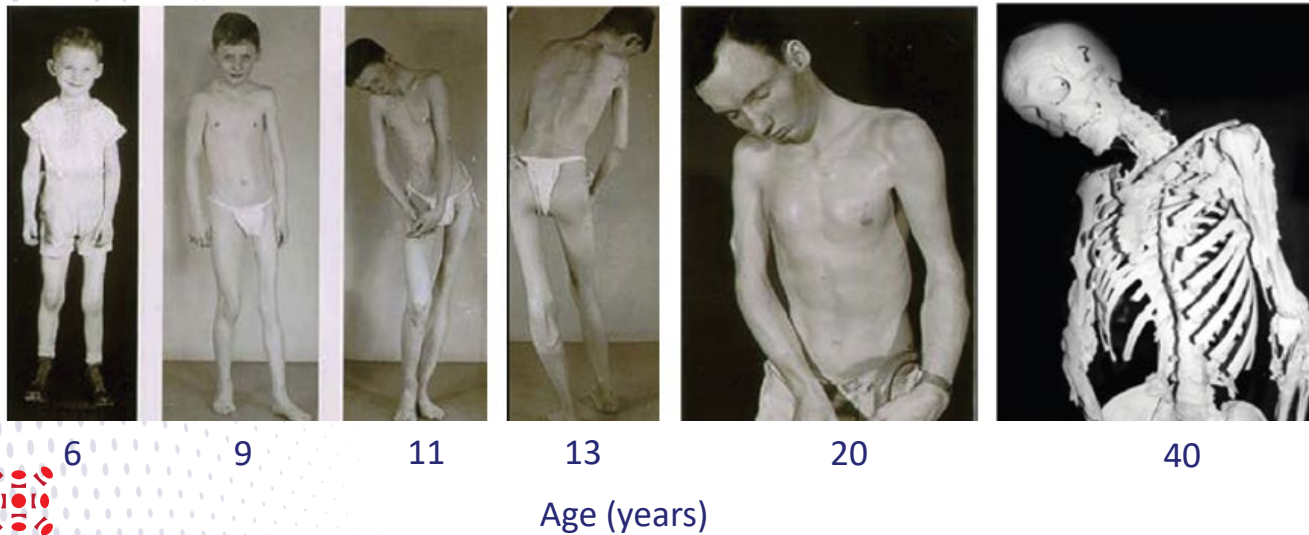




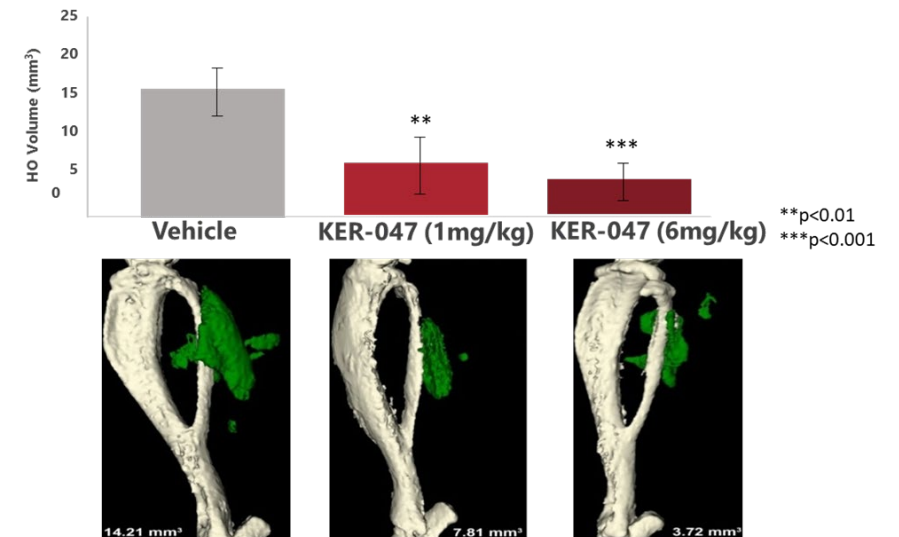
# ALK2 Mutation is a Driver of FOP

- FOP is a rare genetic disease in which muscles and connective tissues transform into bone
- No cure or effective treatments
  - Most patients are confined to a wheelchair by third decade of life
  - Typical life expectancy – 40 years
- Caused by single amino acid mutations in ALK2 that lead to gain-of-function
- KER-047 is designed to target ALK2
  - Preclinical studies conducted in young animals demonstrated that ALK2 inhibition did not result in growth plate ablation or synovial joint malformations

## An example of FOP progression



## KER-047 dose-dependently reduced heterotopic ossification in the genetic mouse model of FOP





# KER-012

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A preclinical program designed to address

- Bone loss disorders such as osteoporosis and osteogenesis imperfecta
- Pulmonary arterial hypertension (PAH)

# KER-012: Preclinical Product Candidate

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- Proprietary selective activin receptor ligand trap in preclinical development for the treatment of pulmonary arterial hypertension (PAH) and bone disorders
- In preclinical studies, KER-012:
  - Demonstrated high affinity for, and potent inhibition of, ligands involved in the regulation of bone homeostasis
  - Increased bone mineral density and trabecular bone volume in wild-type mice and mice with established osteoporosis
  - Did not increase red blood cell production in cynomolgus monkeys
- In a rat model of PAH, rats receiving a rodent version of KER-012 (RKER-012) were protected from the thickening of the right ventricular wall
  - In addition, rats receiving RKER-012 were protected from PAH-associated bone loss
- We believe KER-012 has the potential to increase the signaling of BMP pathways by inhibiting activin A and activin B signaling and, consequently, treat diseases such as PAH that are associated with reduced BMP signaling





# Keros Summary

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# We Believe Keros is Positioned for Clinical and Commercial Success

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- Keros is focused on the development of novel TGF- $\beta$  therapeutics
  - Robust biology that has been validated in the clinic
- Keros is well-positioned to harness the potential of the TGF- $\beta$  superfamily
  - ActRII program (KER-050) is in a Phase 2 trial in patients with MDS and we expect to initiate a Phase 2 trial in patients with MF in 2021
  - Multiple Phase 2 trials for ALK2 program (KER-047) expected to commence in 2021
  - KER-012 is a selective activin receptor ligand trap expected to enter a Phase 1 trial in H2 2021
  - Clinical programs have potentially differentiated mechanism of action
- Our discovery approach has the potential to identify additional molecules with differentiated profiles from existing third-party products and product candidates
  - Pipeline of preclinical assets: bone, muscle and pulmonary



# Anticipated Key Milestones\*

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## KER-050

- Announce initial data for Phase 2 trial in MDS
- Initiate Phase 2 trial in myelofibrosis

Mid-2021  
2021

## KER-047

- Initiate Phase 2 trial in IDA
- Initiate Phase 2 trial in IRIDA

2021  
2021

## KER-012

- Present preclinical data on PAH at major conference
- Initiate Phase 1 trial in healthy volunteers

2021  
H2 2021

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







**Thank You**

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