PRELIMINARY RESULTS OF A PHASE 2 CLINICAL TRIAL OF THE ALK-2 INHIBITOR KER-047 FOR TREATMENT OF IRON REFRACTORY IRON DEFICIENCY ANEMIA

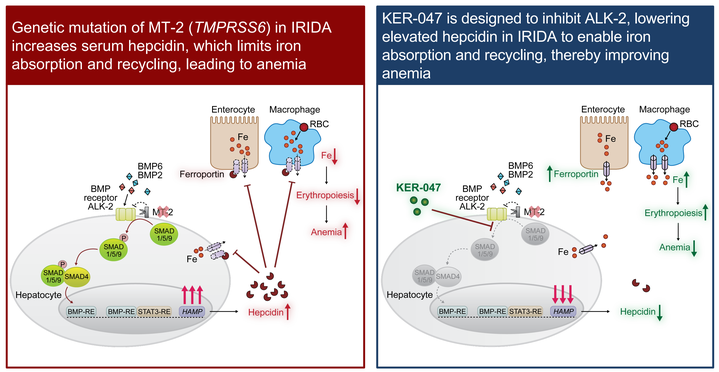
V. Hoving,[1] A.E. Donker,[1,2] H. Natarajan,[3] J. Lachey,[3] S. Cooper,[3] D.W. Swinkels,[1,4] S.E.M. Schols[1]

1. Radboud University Medical Center, Nijmegen, the Netherlands; 2. Máxima Medical Center, Veldhoven, the Netherlands; 3. Keros Therapeutics, Lexington, MA; 4. Sanquin Diagnostics BV, Amsterdam, the Netherlands

INTRODUCTION

- Iron refractory iron deficiency anemia (IRIDA) is a rare autosomal recessive disorder characterized by microcytic anemia with low serum iron and transferrin saturation as well as disproportionately elevated levels of hepcidin, the central hormone that regulates iron, relative to body iron[1]
- IRIDA is caused by a genetic defect in the *TMPRSS6* gene encoding for matriptase-2 (MT-2), a serine protease that suppresses hepcidin secretion by cleaving hemojuvelin, a cell surface coreceptor in the BMP-6 SMAD signaling pathway. This results in increased signaling through the BMP/SMAD pathway, in part mediated by ALK-2 (**Figure 1**)[1-3]
- Excess hepcidin levels in IRIDA reduce iron transport to the plasma by inhibiting the cellular iron exporter ferroportin, resulting in systemic iron deficiency and microcytic anemia[4]
- Currently, there is no targeted therapy treating the underlying disease mechanism. Supportive interventions such as intravenous (IV) iron administration result in iron sequestration in the reticular endothelial system with unknown long-term effects[2]
- Given the central role of aberrant BMP/SMAD signaling in hepcidin production, selective inhibition of the BMP receptor ALK-2 represents a rational approach to target a precipitating factor of IRIDA
- KER-047 is a novel, oral, investigational small-molecule ALK-2 inhibitor
- Preclinical studies in a *TMPRSS6* small interfering RNA knockdown mouse model of IRIDA demonstrated that treatment with a selective ALK-2 inhibitor reversed high hepcidin, increased serum iron, and ameliorated anemia observed in this model[5]
- In a phase 1 clinical trial, administration of KER-047 resulted in decreased serum hepcidin and ferritin and increased serum iron and transferrin saturation (TSAT), consistent with inhibition of ALK-2 signaling (**Figure 2**)[6]
- Here, we present initial safety and tolerability outcomes of an ongoing phase 2 clinical trial of KER-047 in participants with IRIDA (EudraCT 2021-000348-22)

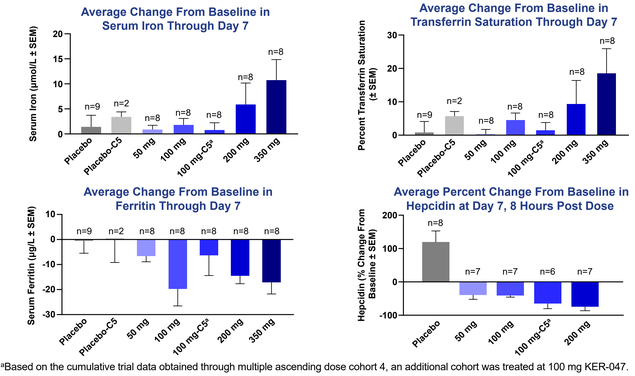
Figure 1. Mechanism of Action of KER-047



ALK-2: activin-like kinase-2; BMP: bone morphogenic protein; Fe: iron; HAMP: hepcidin antimicrobial peptide; IRIDA: iron refractory iron deficiency anemia; MT-2: matriptase-2; RBC: red blood cell; RE: responsive element; SMAD: mothers against decapentaplegic homologs.

INTRODUCTION (cont.)

Figure 2. Administration of Multiple Doses of KER-047 in a Phase 1 Clinical Trial (KER-047-01) in Healthy Volunteers Resulted in Increases in Serum Iron and Transferrin Saturation and Decreases in Ferritin and Hepcidin Consistent With Inhibition of ALK-2 Signaling[6]

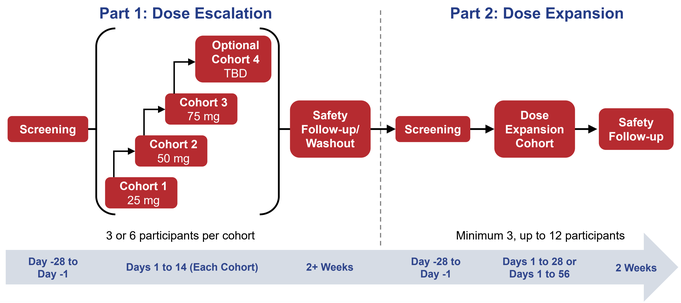


[a]Based on the cumulative trial data obtained through multiple ascending dose cohort 4, an additional cohort was treated at 100 mg KER-047.

METHODS

- KER-047-IR-201 is a 2-part, open-label dose-escalation and dose-expansion trial (**Figure 3**)
  - Part 1 is a dose-escalation phase consisting of up to 4 ascending-dose cohorts starting at 25 mg once daily, and Part 2 is a dose-expansion phase with treatment dose and duration based on Part 1 outcomes
  - Participants are allowed to go through multiple dose escalations and can participate in Part 1 and Part 2 of the clinical trial
  - Safety is the primary objective; secondary objectives include pharmacokinetic and pharmacodynamic analyses
- Key eligibility criteria
  - Diagnosis of IRIDA based on a homozygous or compound heterozygous *TMPRSS6* genotype
  - TSAT <15%
  - Ferritin level of 50-700 µg/L
  - Hemoglobin <13.8 g/dL (males) or <12.7 g/dL (females)
  - C-reactive protein <10 mg/L
  - Have not received IV iron treatment within 28 days prior to trial entry
- Participants will be treated once daily with KER-047 for a 2-week period followed by a 2-week washout period
- Data will be analyzed by descriptive statistics

Figure 3. KER-047-IR-201 Phase 2 Clinical Trial Design



RESULTS

- One participant has enrolled in the first dose-escalation cohort (KER-047 25 mg once daily)

Safety

- The participant reported a treatment-emergent adverse event of intermittent dizziness, which was determined to be unrelated to the study drug
- No serious adverse events or dose-limiting toxicities were observed during treatment

Clinical Outcomes

- TSAT/hepcidin ratio slightly increased during treatment but returned to baseline levels after the 2-week treatment period (**Table 1**)
- Ferritin levels decreased during the 2-week treatment period and returned to baseline levels in the washout period (**Figure 4A**)
- Reticulocyte hemoglobin content (Ret-He) increased by day 5 of treatment (**Figure 4B**)
- Hemoglobin concentration and mean corpuscular volume remained stable (**Table 1**)

Laboratory Results Before, During, and After Administration of KER-047 for the First Low-Dose Cohort (n=1; Figure 4, Table 1)

Figure 4.

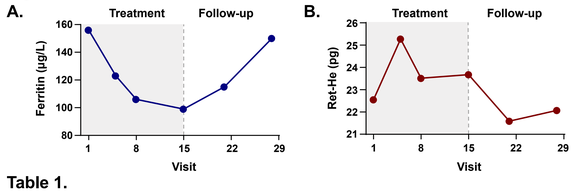


Table 1.

	Predose (Day 1)	Day 5	Day 8	Day 15	Day 21	Day 28
KER-047	--	25 mg QD	25 mg QD	Follow-up	Follow-up	Follow-up
Hepcidin, nM	5.9	np	2.4	4.7	np	np
TSAT, %	5.2	4.9	5.6	4.6	6.6	3.8
TSAT/hepcidin, %/nM	0.88	np	2.33	0.98	np	np
MCV, fl	70	71	72	72	73	73
Hb, g/dL	12.6	12.1	12.4	12.9	12.9	12.6

Hb: hemoglobin; MCV: mean corpuscular volume; np: not performed; QD: once daily; Ret-He: reticulocyte hemoglobin; TSAT: transferrin saturation.

SUMMARY

- In this phase 2 clinical trial of the novel ALK-2 inhibitor KER-047, a dose of 25 mg once daily was generally well tolerated in one participant enrolled thus far
  - Two additional participants are scheduled for screening to complete the first dose cohort
- The observed decreases in ferritin as well as in hepcidin in this participant were consistent with observed changes in response to KER-047 administration in the phase 1 clinical trial
- The laboratory parameters involved in erythropoiesis appeared to improve, suggestive of iron redistribution consistent with KER-047's mechanism of action
- KER-047 has the potential to address the root cause of IRIDA by reducing the iron-sensing hepcidin signaling axis in the hepatocyte by inhibiting the overactive ALK-2 signaling pathways, leading to redistribution of iron stores from the reticuloendothelial system and increasing iron availability for erythropoiesis
- This trial is actively recruiting to further investigate KER-047 as an agent to potentially address an underlying cause of IRIDA

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CONTACT INFORMATION

PI: S.E.M. Schols
Saskia.Schols@radboudumc.nl

https://www.kerostx.com/
EudraCT 2021-000348-22

Investors: Deepankar Roy,
droy@kerostx.com
+1 (213) 268-1878