A Phase 2, Open-label, Dose Escalation and Dose Expansion Study of KER-047 for the Treatment of IRIDA

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Primary Objectives: • To evaluate the safety and tolerability of ascending doses of KER 047 in participants with iron-refractory iron deficiency anemia (IRIDA)Secondary Objectives:• To evaluate the pharmacodynamic (PD) effects of KER 047 on iron...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54150

Source
ToetsingOnline

Brief title
IRIDA Study of KER-047

Condition

- Other condition
- Red blood cell disorders
- Blood and lymphatic system disorders congenital

Synonym
IRIDA, iron-refractory iron deficiency anemia

Health condition

iron-refractory iron deficiency anemia (IRIDA)

Research involving

Human

Sponsors and support

Primary sponsor: Keros Therapeutics, Inc.
Source(s) of monetary or material Support: Keros Therapeutics;Inc.

Intervention

Keyword: anemia, Dose Escalation, IRIDA

Outcome measures

Primary outcome

Safety Endpoints:

• Safety and tolerability as determined by the incidence of treatment-emergent adverse events (TEAEs), dose limiting toxicities (DLT's), treatment related serious AEs, and discontinuations due to AEs; and change from baseline in clinical laboratory values, vital signs, and electrocardiogram (ECG)

Pharmacodynamic Endpoints:

The following laboratory values will be assessed as change from baseline after 28 days of treatment in Part 1 and after 28 or 56 days of treatment in Part 2:

• Hepcidin concentration in plasma

• Serum iron

• Ferritin

• Total iron binding capacity (TIBC)

• Transferrin saturation (TSAT)

• Reticulocyte hemoglobin content (RET-He/CHr)

• Soluble transferrin receptor (sTfR) and sTfR/log ferritin index

• TSAT/hepcidin; ferritin/hepcidin

Pharmacokinetic Endpoints:

The following parameters for KER-047 and any metabolites of interest will be assessed in Part 1 on Days 8, 15, 22, and 29, and in Part 2 on Days 8, 15, 22, and 29 if treatment was 28 days or Days 8, 15, 22, 29, 36, 43, 50, and 57 if treatment was 56 days:

• Trough plasma concentraion (Ctrough)

• Plasma accumulation (Rac)

Secondary outcome

Exploratory Endpoints:

• Proportion of participants who have a response, defined as a hemoglobin increase of >= 1.5 g/dL (0.9 mmol/L) from baseline after 28 days of treatment in Part 1 and 28 or 56 days of treatment in Part 2. Proportion of participants who have a response, defined as a hemoglobin increase of >= 1.0 g/dL (0.6 mmol/L) from baseline after 28 days of treatment in Part 1 and 28 or 56 days of treatment in Part 2.

• Change from baseline in hemoglobin after 28 days of treatment in Part 1 and 28 or 56 days of treatment in Part 2

• Change from baseline in hemoglobin after 14 days of treatment in Part 1 and 28 or 56 days of treatment in Part 2.

• Change from baseline in red blood cell indices (mean corpuscular volume [MCV], mean corposcular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), and reticulocyte count after 28 days of treatment in Part 1 and 28 or 56 days of treatment in Part 2.

• Change from baseline in health-related quality of life as measured by SF-36 after 28 days of treatment in Part 1 and 28 or 56 days of treatment in Part 2.

Study description

Background summary

Iron is required to synthesize hemoglobin for maturing red blood cells (RBCs). Most iron is recycled by hepatic and splenic macrophages after phagocytosis of senescent RBCs, while a small amount is absorbed daily by duodenal enterocytes. Hepcidin is the iron-regulatory protein hormone produced by hepatocytes, which negatively regulates serum iron by inducing internalization and degradation of the only known iron exporter protein, ferroportin. Liver sinusoidal endothelial cells sense iron-loaded transferrin and ferritin levels in serum and regulate hepcidin production through the bone morphogenetic protein (BMP) pathway, especially BMP2 and BMP6. Increased hepcidin results in reduced iron absorption by the duodenum, and reduced release of iron from liver and iron-recycling macrophages.1
Anemias may be classified based on the presence of high or low hepcidin. Iron-deficient and iron-loading anemias have low hepcidin levels. In contrast, iron-refractory iron deficiency anemia (IRIDA), hepcidin-producing adenoma-associated anemia, and anemia of inflammation (also known as anemia of chronic disease) are characterized by high hepcidin levels. Disorders with anemia and iron overload secondary to chronic transfusions, such as β-

thalassemia major
are also associated with elevated hepcidin.
IRIDA is a rare, inherited form of iron deficiency anemia that results from loss of function
mutations in the TMPRSS6 gene,2 which encodes for matriptase-2 (MT-2), a transmembrane
serine protease that cleaves hemojuvelin from hepatocytes resulting in inhibition of hepcidin.
Decreased activity of MT-2 results in elevated activin receptor-like kinase 2 (ALK2) signaling
and high hepcidin levels.3 Patients with IRIDA are usually diagnosed in childhood, presenting
with mild to moderate anemia. Since most children with IRIDA exhibit normal growth and
development, the anemia is usually detected in the process of routine screening. Signs and
symptoms associated with iron deficiency, such as koilonychias or hair loss, and anemia, such as
fatigue, weakness, and shortness of breath, are rare. Hematologic examination shows a
reticulocytopenic, hypochromic, microcytic anemia, with disproportionately low mean
corpuscular volume (MCV) with respect to the degree of anemia. Iron biomarkers show low
transferrin saturation, and low serum iron that is only partially responsive to oral and parenteral
iron, due to poor absorption and defective utilization.3
Currently, there are no therapies approved for the treatment of IRIDA, and those that are used are
not without side effects. High-dose oral iron is difficult to tolerate due to gastrointestinal (GI)
effects. Intravenous (IV) iron has restrictive and time-consuming administration requirements
which results in underutilization. Blood transfusion may be used as a last resort treatment for
severe symptomatic anemia, but is generally to be avoided due to transfusion-associated risks.3,4
Therefore, there is an unmet need for more effective, safer, and more convenient treatments for
IRIDA.
Studies conducted in a TMPRSS66 siRNA knockdown mouse model of IRIDA demonstrated
that KER-047 treatment resulted in reduced hepcidin, increased serum iron, and ameliorated
anemia. Thus, KER-047, via inhibited hepcidin expression and increased iron mobilization, has
the potential to benefit patients with anemia related to high hepcidin, such as

IRIDA.

Study objective

Primary Objectives:
• To evaluate the safety and tolerability of ascending doses of KER 047 in participants with iron-refractory iron deficiency anemia (IRIDA)
Secondary Objectives:
• To evaluate the pharmacodynamic (PD) effects of KER 047 on iron metabolism in participants with IRIDA
• To evaluate plasma accumulation of KER 047 across the treatment period
Exploratory Objectives:
• To evaluate the effect of KER 047 on anemia in participants with IRIDA
• To evaluate the effect of KER 047 on health-related quality-of-life as measured by the 36-Item Short Form Survey (SF 36)

To evaluate the safety and tolerability of ascending doses of KER--047 in participants with IRIDA

Study design

Study Design:
This is a phase 2, two-part, open-label, intra-participant dose escalation and dose expansion study to evaluate the effects of KER-047 in participants with IRIDA. Participants may enroll in Part 1, in and/or Part 2 only, or in both parts. Part 1 (dose escalation) is planned to be 3 ascending dose levels. An optional additional level may be added at the recommendation of the Safety Review Committee (SRC); see Dose Escalation description, below. Part 2 (Dose Expansion) is planned to be an expansion with dose level selected based on review of the data from Part 1.

Intervention

KER-047 is a powder for oral suspension and will be suspended in water to produce an in-use suspension for oral dosing.

Study burden and risks

The burden and risk mainly consist of extra time spent compared to standard treatment, the use of KER-047 and the risks of medical evaluation, including venipuncture.

Potential Risks:
• Increased fracture risk. Increased risk of joint inflammation.
• Abdominal discomfort, weight loss, constipation, gastroenteritis, nausea and vomiting, gastric ulceration

• Corneal erosions, eye pain
• Acute kidney injury, proteinuria, hematuria
• Macro- and micro-vasculitis
• Liver enzyme increase
• Lymphopenia, neutropenia

Please refer to 25 of the protocol, Table 2 for proposed mitigation and monitoring of these risks

Contacts

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Scientific
Keros Therapeutics, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Participants are eligible for the study if all of the following criteria apply:
1. Male or female >= 18 years of age, at the time of signing informed consent.

2. Confirmed diagnosis of IRIDA based on the following:
- Documented homozygous or compound heterozygous TMPRSS6 gene variant(s) of Class 3 or greater (variant of uncertain significance, likely pathogenic, pathogenic) per the Association for Clinical Genomic Science.
3. Serum TSAT at screening less than 15%.
4. Participants receiving oral iron supplementation must be on a stable dose for >=4 weeks prior to Day 1, with a maximum of 60 mg/day of oral elemental iron. Intravenous (IV) iron is not permitted during the study.
5. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local study participant privacy regulations.
6. Females of childbearing potential and sexually active males must agree to use effective methods of contraception as outlined in the protocol.
7. In the opinion of the Investigator, the participant is able and willing to comply with the requirements of the protocol (e.g., all study procedures, return for follow-up visits).

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:
Medical History
1. Body mass index >35 kg/m2
2. Any active infection requiring parenteral antibiotic therapy within 28 days prior to Day 1 or oral antibiotics within 14 days of Day 1. Any infection with >5 days of fever (> 38.5* C) within 28 days prior to Day 1.
3. Presence of uncontrolled heart disease or New York Heart Association Class 3 or 4 heart failure.
4. History or presence at screening of an uncontrolled chronic disease.
5. History of drug or alcohol abuse, as defined by the investigator, within the past 2 years.
6. History of stroke, arterial embolism, or unresolved deep venous thrombosis within 6 months prior to Day 1.
7. Major surgery within 28 days prior to Day 1. Participants who had surgery more than 28 days prior to Day 1 must have recovered satisfactorily to participate in the study, in the opinion of the Investigator.
8. Known positive for human immunodeficiency virus, active infectious hepatitis B, or active infectious hepatitis C.
9. Any malignancy that has not been in remission and/or has required systemic therapy including radiation, chemotherapy, hormonal therapy, or surgery within the last year prior to Day 1.
10. History of solid organ or hematological transplantation.
11. Have had a fracture within 4 weeks of D1.
12. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the IMP.

Treatment History
13. Treatment with IV iron within 28 days prior to study entry.
14. Receiving treatment with proton pump inhibitors (PPIs). Participants receiving PPIs who discontinue use at least 7 days prior to Day 1 are permitted to enroll.
15. Receiving and plan to continue any disallowed medications.
16. Treatment with another investigational drug or device, or approved therapy for investigational use <= 28 days prior to Day 1, or, if the half-life of the previous product is known, within 5 times the half-life prior to Day 1, whichever is longer.

Laboratory Exclusions
17. Hemoglobin level >=13.8 g/dL (8.56 mmol/L) (males) or >=12.1 g/dL (7.51 mmol/L) (females)
18. Serum ferritin < 50 or > 500 µg/L
19. Absolute lymphocyte count < 1.00 x 109/L
20. Absolute neutrophil count < 1.50 x 109/L
21. Estimated glomerular filtration rate by Chronic Kidney Disease-Epidemiology Collaboration creatinine equation < 45 mL/min/1.73 m2
22. Alanine transaminase or aspartate transaminase > 2 x upper limit of normal (ULN)

Miscellaneous
23. Pregnant or lactating females.
24. Any other condition not specifically noted above that, in the judgment of the Investigator or Sponsor, would preclude the participant from participating in the study.
25. Participants who are investigational site staff members directly involved in the conduct of the trial and their immediate family members, site staff members otherwise supervised by the Investigator, or participants who are Keros or CRO employees directly involved in the conduct of the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-02-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KER-047
Generic name:	KER-047

Ethics review

Approved WMO Date:	20-04-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-08-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-04-2022
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-04-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	2021-000348-22
EudraCT	EUCTR2021-000348-22-NL
CCMO	NL77168.091.21

Study results

Results posted: 22-11-2023

Actual enrolment: 1

First publication
25-10-2023