Short title: KER-047 for the Treatment of IRIDA

Principal investigator: Saskia Schols

Sponsor: Keros Therapeutics

EudraCT nr. (if applicable):

Patient population: Adult patients (≥ 18 years) with IRIDA (genetically confirmed)

Required no. of patients (if applicable): 9 - 12

Type of study: A Phase 2, Open-label, Dose Escalation and Dose Expansion Study of

KER-047 for the Treatment of IRIDA

Study objectives:

Primary objectives: To evaluate the safety and tolerability of ascending doses of KER-047 in participants with ironrefractory 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

Subject eligibility criteria:

Inclusion criteria:

1. Male or female ≥ 18 years of age, at the time of signing informed consent.
2. 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 (VUS), likely pathogenic, pathogenic) per the Association for Clinical Genomic Science (ACGS).
3. Serum TSAT at screening <10%.
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:

Medical History

1. Body mass index (BMI) >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^{o} 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 of uncontrolled hyper- or hypothyroidism.
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 (DVT) 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 (HIV), active infectious hepatitis B (HBV), or active infectious hepatitis C (HCV).
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. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational drug.
12. History of corneal dysplasia.
13. History of any known inflammatory or immunodeficiency disorder (e.g., lupus, common variable immunodeficiency [CVID]).

Treatment History

14. Treatment with IV iron within 28 days prior to study entry
15. 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.
16. Receiving and plan to continue any disallowed medications listed in the protocol.
17. 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

18. Hemoglobin level ≥13.8 g/dL (8.56 mmol/L) (males) or ≥12.1 g/dL (7.51 mmol/L) (females)
19. Serum ferritin <50 or >500 µg/L
20. Absolute lymphocyte count <1.00 x 109/L
21. Absolute neutrophil count <1.50 x 109/L
22. Estimated glomerular filtration rate (eGFR) by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation < 45 mL/min/1.73 m2
23. Alanine transaminase (ALT) or aspartate transaminase (AST) >1.5x upper limit of normal (ULN)
24. C-reactive protein (CRP) ≥10 mg/L

Miscellaneous

25. Pregnant or lactating females.

26. 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.

Status: Open in Radboudumc (monocenter in The Netherlands)

Participating sites: Radboudumc only

Contact for more information:

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Summary (optional):

Treatment Plan:
Part 1:

Cohort	**KER-047 DoseLevel***	**Number of Participants****
1	25 mg qd x 14 days	3 or 6
2	50 mg qd x 14 days	3 or 6
3	75 mg qd x 14 days	3 or 6
4 (optional)	TBD mg qd x 14 days	3 or 6

Planned Total: Approximately 12

*KER-047 dose level for Cohort 1 is 25 mg. The dose level for all subsequent cohorts will be recommended by the SRC per the dose escalation scheme. Dose may be escalated or deescalated by the SRC. Regimen may be altered by the SRC.
**The SRC will determine whether a cohort should be expanded to 6 participants.

Part 2:

Cohort	**KER-047 Dose Level***	**Number of Participants**
1	TBD mg qd x 28 or 56 Days.	Minimum 3, up to 12

*KER-047 dose level and duration (28 or 56 days) for Part 2 will be