

**Protocol Number:** TAK-226-3001



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**Letter No.:** QR/RA/QAB41954/2026/01

**Date:** 04 Feb 2026

**To,**

The Drugs Controller General (India)  
Directorate General of Health Services  
FDA Bhavan, Kotla Road  
New Delhi 110 002

**Protocol Number:** TAK-226-3001 Original Protocol dated 01 Sep 2025

**Protocol Title:** A Phase 3, Multicenter, Open-Label, Randomized Trial to Compare the Efficacy and Safety of Elritercept versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in ESA-naïve Adult Participants Who Require Red Blood Cell Transfusions

**Subject:** Global Clinical Trial application under New Drugs and Clinical Trials Rules, 2019, seeking:

1. **Permission to conduct Phase 3 Global Clinical Trial in Form CT-04**
2. **Test License for import of Investigational Products (IP) in Form CT-16**

Dear Sir,

On behalf of **Takeda Development Center (TDC) Americas, Inc., USA**, we are submitting herewith this application in **Form CT-04** seeking your permission to conduct a global clinical trial titled, " A Phase 3, Multicenter, Open-Label, Randomized Trial to Compare the Efficacy and Safety of Elritercept versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in ESA-naïve Adult Participants Who Require Red Blood Cell Transfusions " per New Drugs and Clinical Trials Rules, 2019.

**Letter of Authorization** from Takeda Development Center (TDC) Americas, Inc., 500 Kendall Street Cambridge, MA 02142, USA to IQVIA RDS (India) Pvt. Ltd. India is enclosed with the application (**Enclosure 1.4**).

This study will be conducted in compliance with the Study Protocol, the International Council for Harmonization (ICH) Good Clinical Practice (GCP) and Indian GCP guidelines, and with all applicable rules, guidelines and current regulatory requirements in India. The study will be performed as a multi-national, multi-center, randomized, double-blind study in accordance with the protocol enclosed.

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## **RATIONALE FOR CONDUCTING THE STUDY**

MDS in India tends to present around the mid-50s, roughly a decade earlier than in Western cohorts where median age at diagnosis is ~70.<sup>13</sup> A tertiary center study in eastern India reported a median age of 55 years among MDS patients, and a large multi-year cohort from CMC, Vellore had a median age of 53.<sup>13,14</sup> This earlier onset is similar to observations across Asia that MDS occurs ~10 years younger than in the West. Despite the clinical significance of Myelodysplastic Syndromes (MDS), there is currently no comprehensive national data on its incidence or prevalence in India, highlighting a critical gap in epidemiological surveillance and cancer registry reporting.

A study from a center in Kolkata reported that 96.6% of MDS patients eventually required blood transfusion support, primarily for anemia or thrombocytopenia.<sup>13</sup> Indian patients appear to be transfusion-dependent at or shortly after diagnosis.<sup>13</sup> This aligns with international data indicating that approximately 80-90% of MDS patients are anaemic and approximately half of these patients become red blood cell (RBC) transfusion-dependent during the course of their illness.

The rationale for conducting the study in India [including Unmet medical need in the country] Justification for selected dose and treatment duration, Rationale for inclusion of patients who are more than 65 years of age has been presented in **Enclosure 1.7**.

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## **INVESTIGATIONAL PRODUCT**

### **Investigational medicinal product - TAK-226:**

Elritercept (TAK-226) drug product is a liquid solution intended for subcutaneous (SC) injection. The dosing regimen involves administration at 3.75 mg/kg, with up-titration to 5.0 mg/kg, SC every 4 weeks (Q4W).

Based on response criteria and safety/tolerability. The dose of elritercept may be down-titrated per protocol, if needed, for an increase in hematology parameters or AEs.

The Investigational Medicinal Product, Elritercept (KER-050, TAK-226) is a recombinant fusion protein designed to inhibit signaling by select TGF- $\beta$  superfamily ligands, including activin A, activin B, GDF 8, and GDF 11.

Elritercept is not a narcotic, psychotropic, radiopharmaceutical and neither consists of nor contains genetically modified organisms, nor is it an ATMP.

“The IMPD includes a Placebo Module, however, Placebo is not used in the current trial. “

### **Reference Therapy and Dosage:**

Epoetin alfa 450 IU/kg starting dose once a week (Q1W).

The corresponding SmPC is provided with this application for details and reference to the marketing authorization of the product.

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OVERALL STUDY DESIGN

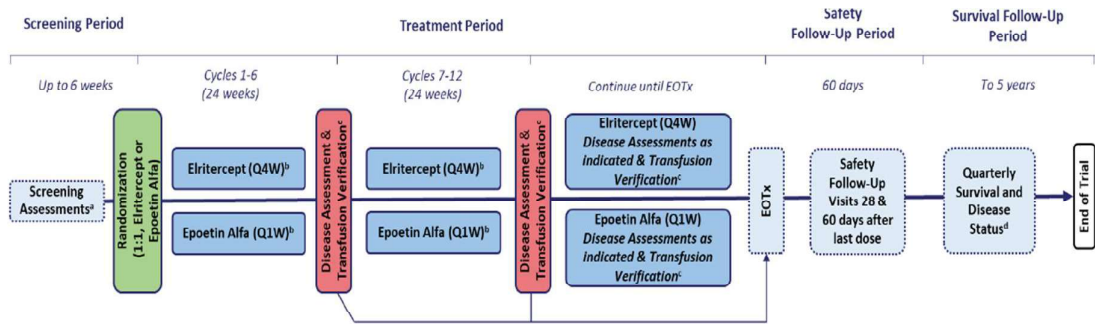
This is a registrational, phase 3, multicenter, randomized, open-label, active-controlled, parallel-arm, interventional trial to evaluate the efficacy and safety of elritercept versus epoetin alfa for treatment of transfusion-dependent anemia in ESA-naïve adult participants with very low-, low-, or intermediate-risk MDS (LR-MDS according to classification by 2012 IPSS-R).

The primary objective is to evaluate the efficacy of elritercept on red blood cell transfusion independence (RBC-TI) for a minimum 12-week period within 24 weeks with concurrent mean hemoglobin (Hgb) increase  $\geq 1.5$  g/dL compared to epoetin alfa.

The trial will consist of the following phases:

- Screening period: Up to 42 days prior to randomization, but it may be extended to confirm eligibility
- Treatment period: At least 24 weeks. After 24 weeks, an MDS Disease Assessment will be conducted, and treatment may continue until discontinuation per protocol
- Posttreatment follow-up period: At least 5 years from the date of the first dose of trial intervention.

A schematic of the study design is presented in Figure 1.



AE: adverse event; AML: acute myeloid leukemia; C1D1: Cycle 1 Day 1; C3D1: Cycle 3 Day 1; EOTx: end of treatment; MDS: myelodysplastic syndrome(s); Q1W: once a week; Q4W: every 4 weeks; SFU: survival follow-up.

<sup>a</sup> Screening assessments to be completed within 6 weeks prior to randomization, and may be extended by 2 weeks for a total of 8 weeks to complete transfusion history if needed and/or up to an additional 6 weeks for a total of 12 weeks for central pathology review of bone marrow for eligibility.

<sup>b</sup> Elritercept and epoetin alfa to be administered in 28 day cycles. The starting dose will be used through C3D1 and up-titrated based on response criteria and safety/tolerability. Dose decrease may be required per protocol for an increase in hematology parameters or AEs. See Section 6.3

<sup>c</sup> All participants complete collection of all RBC and platelet transfusions data after first dose until the next transfusion date after EOTx. If the participant had an EOTx visit before 24 weeks, continue to record transfusion data through 24 weeks; if no transfusions were reported between EOTx and 24 weeks, then monitor until the next transfusion date. Participants on treatment complete bone marrow collection for the MDS Disease Assessment at 24 and 48 weeks after C1D1.

<sup>d</sup> Survival Follow-Up will assess survival status, determine the start and end dates of subsequent MDS treatments, date of progressive disease to AML (when applicable), and collect EQ-5D-5L for 5 years from randomization withdrawal from trial, whichever is earliest.

Overall, benefit-risk assessment of the trial is provided in section 2.5 of the protocol.

STUDY HIGHLIGHTS

Primary objective

- To evaluate the efficacy of elritercept on red blood cell transfusion independence (RBC-TI) for a minimum 12-week period within 24 weeks with concurrent mean hemoglobin (Hgb) increase  $\geq 1.5$  g/dL compared to epoetin alfa.

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### **Secondary objective**

- Key Secondary Objective: To compare the effect of elritercept on RBC-TI for a minimum 16-week period within 24 weeks versus epoetin alfa.
  - Key Secondary Objective: To compare effect of elritercept on RBC-TI for a minimum 12-week period within 24 weeks versus epoetin alfa.
  - Key Secondary Objective: To compare the effect of elritercept on RBC-TI for a minimum 24-week period within 24 weeks versus epoetin alfa.
  - To compare the effect of elritercept versus epoetin alfa on favorable fatigue response with absence of RBC transfusion between the end of Week 12 and the end of Week 24.
  - To compare effect of elritercept on hematological improvement-erythroid (HI-E) for a minimum 8-week and for a minimum 12-week period within 24 weeks and within 48 weeks versus epoetin alfa.
  - To compare the effect of elritercept on RBC-TI at multiple time periods: for a minimum 8-week period within 24 weeks, and for a minimum 24-week period within 48 weeks versus epoetin alfa.
  - To compare time to achieve RBC-TI for a minimum 12 weeks and a minimum 16 weeks RBC-TI within 24 weeks for participants receiving elritercept versus epoetin alfa.
  - To compare the effect of elritercept on mean Hgb change through 24 and 48 weeks.
  - To compare duration of RBC-TI  $\geq 12$  weeks and  $\geq 16$  weeks RBC-TI achieved within 24 weeks for participants receiving elritercept versus epoetin alfa.
  - To compare RBC transfusion burden during treatment for participants receiving elritercept versus epoetin alfa.
  - To compare time to receive first RBC transfusion for participants receiving elritercept versus epoetin alfa.
  - To compare time to achieve HI-E for a minimum 8 weeks within 24 weeks for participants receiving elritercept versus epoetin alfa.
  - To compare the effect of elritercept versus epoetin alfa on health-related quality of life (HRQoL).
  - To describe the plasma concentration-time data to contribute to population pharmacokinetics and exposure-response analyses of elritercept.
  - To evaluate antidrug antibodies (ADA) in response to elritercept treatment.
  - To compare time to progression to acute myeloid leukemia (AML) in participants treated with elritercept compared to epoetin alfa.
  - To assess overall survival of participants treated with elritercept versus epoetin alfa.
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### **Planned Sample Size**

Approximately 210 to 300 participants will be enrolled in this study from approximately 150 trial sites globally. Participants deemed eligible for the trial will be randomized 1:1 to either elritercept or epoetin alfa by a central randomization procedure using IRT.

The study is proposed to be conducted with a target of enrolling 30 subjects from India.

### **Trial Duration**

#### **Total duration of trial intervention for each participant:**

A planned minimum of 24 weeks of trial intervention to demonstrate efficacy. The total duration of treatment will vary depending on the participant's response to treatment or toxicity or other reasons for discontinuation are met.

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**Total duration of trial participation for each participant:**

Approximately 5 years from randomization.

The expected total duration of the trial is approximately 8 years. This includes approximately 3 years of enrollment, and 5 years from last randomized participant. The duration of participation for a participant will be approximately 5 years from randomization.

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**Regulatory Status of Study Protocol TAK-226-3001 in other participating countries:**

The clinical trial is proposed to be conducted in **28 countries**: Argentina, Australia, Brazil, Canada, Japan, Korea, Malaysia, Mexico, Taiwan, Thailand, Turkey, United Kingdom, United States, Belgium, Bulgaria, France, Germany, Greece, Hungary, Ireland, Italy, **India**, Lithuania, Netherlands, Norway, Poland, Romania, Spain.

Regulatory and Enrollment Status in Participating Countries and copy of approval letters from USA and South Korea enclosed in Section 1.9.2.2 for your reference only.

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**TEST LICENCE APPLICATION**

Investigational Medicinal Product - TAK-226 and RETACRIT® (epoetin zeta) will be imported from:

Almac Clinical Services  
4204 Technology Drive Durham,  
NC 27704, USA

And / Or

Almac Clinical Services Limited  
Seagoe Industrial Estate,  
9 Charlestown Road, Craigavon,  
Northern Ireland, BT63 5PW,  
United Kingdom

We are hereby providing the below listed documents for application of Test License for the reference study:

- CT-16 along with e-Challans (**Enclosure 1.3.3**)
- Justification for quantity of study drugs to be imported (**Enclosure 1.3.4**)
- Copy of GMP certificates and QP declaration (**Enclosure 3.3**)

**Products labelling**

Only the name and address of the sponsor is provided with the labels. Trial subjects will receive a patient ID card, which they are instructed to keep in their possession always. This ID card provides contact details including phone number of the investigator and an additional 24-hour phone assistance number provided by the sponsor for health care professionals for this clinical trial.

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With regards to the batch number, the Sponsor confirms that the product batch numbers will be included on the labels prior to the release in the appropriate placeholder i.e., under “lot number”.

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## **PARTICIPATING SITES AND ETHICS COMMITTEES**

A total of **07 Principal Investigators** from India is proposed to participate in the clinical trial. The list of the Principal Investigators, their Undertakings and CVs are enclosed in **Enclosure 7.7.2**.

All clinical trial sites are multi-specialty and have registered Institutional Ethics Committee (EC) and have adequate emergency facilities. Please refer to **Enclosure 7.7** for additional details. Kindly note that all participating sites have adequate facility to perform audio-visual recording of informed consent processes.

The participating Investigators are in process of submitting the essential documents to their respective Ethics Committees. We will submit the Ethics Committee approvals once they are available.

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We thank you for your consideration and look forward to your **approval to conduct the clinical trial** in India under **TAK-226-3001 Original Protocol** dated 01 Sep 2025, at the proposed clinical trial sites, and to receive the **Test License** to import the study medication in India.

Thanking you,

**For IQVIA RDS (India) Pvt. Ltd.**

Signed by:  Signed by: 

 Signed by Sneha Gupta  
*Sneha Gupta* | I approve this document  
04-Feb-2026 | 5:44:04 AM PST

011152F42AFF4780AC7BF2F140A595E7  
Sneha Gupta  
Director, Regulatory Affairs  
Mobile: + 91 995 888 1837; Email: sneha.gupta2@iqvia.com

## **MODULE I: ADMINISTRATIVE SECTION**

- 1.1 Annexure Sheet
- 1.2 Covering Letter
- 1.3 Forms and Challans
  - 1.3.1 Annexure A (Export NOC)
  - 1.3.2 Details about the Central Lab
  - 1.3.3 Form – CT-16 & e-Challan Details
  - 1.3.4 Justification for Quantities of Study Drugs to be Imported dated 06 Jan 2026
- 1.4 Letter of Authorization dated 03 Dec 2025
- 1.5 Name and Address of the Sponsor

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- 1.6 Name and Address of the Legal Applicant (Filing the application)
- 1.7 Rationale for Conducting the study; Rationale for Conducting the study in India (including Assessment of Risk Vs Benefits to the Patients, Unmet Medical Need in the Country); Justification for selected Dose and treatment Duration; Justification for Inclusion of Patients above 65 years of age and Innovation vis a vis existing therapeutic options dated 24 Jan 2026
- 1.8 Drug Details
- 1.9 Study Details:
  - 1.9.1 Phase of Study
  - 1.9.2 Global Details
    - 1.9.2.1 Names of the participating countries
    - 1.9.2.2 Regulatory and Enrollment Status of the study in other participating countries dated 26 Jan 2026 along with the other participating countries RA approvals
    - 1.9.2.3 Total Number of Patients to be enrolled globally
    - 1.9.2.4 Affidavit declaring that the study has not been discontinued in any country. In case of discontinuation the reasons for such a discontinuation would be communicated dated 17 Dec 2025
    - 1.9.2.5 Declaration on no Clinical Trial of the Investigational Product has been Withdrawn/Discontinued in any country or rejected/refused by any Regulatory Agency dated 16 Dec 2025
  - 1.9.3 India Details
    - 1.9.3.1 Total Number of Patients to be enrolled in India
    - 1.9.3.2 Letter of Undertaking by Takeda Development Center (TDC) Americas, Inc., USA regarding marketing of the Elritercept (TAK- 226) in India dated 17 Dec 2025

**MODULE II: SUMMARIES**

- 2.1 Executive Summary & Enclosures
- 2.2 Protocol Synopsis
- 2.3 Clinical Development for Proposed Indication and any other Indication

**MODULE III: CMC DATA**

- 3.1 Investigational Medicinal Product Dossier (IMPD) Version 5.0 for TAK-226 dated 18 Jul 2025
- 3.2 Certificate of Analysis- Drug Substance, Drug Product and Comparator
- 3.3 QP declarations and GMP certificates
- 3.4 TSE declarations
- 3.5 Comparator - Retacrit Simplified IMPD (sIMPD) V1.0\_Final
- 3.6 Comparator - EU SmPC Epo\_retacrit epar product information

**MODULE IV: ANIMAL TOXICOLOGY DATA**

- 4.1 Systemic Toxicity Studies
  - 4.1.1 Single Dose Toxicity
  - 4.1.2 Repeated Dose Toxicity
- 4.2 Male Fertility Study
- 4.3 Female Reproduction and Developmental Toxicity Studies

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**4.4 Local Toxicity**

- 4.4.1 Dermal Toxicity
- 4.4.2 Ocular Toxicity
- 4.4.3 Inhalation Toxicity
- 4.4.4 Vaginal Toxicity
- 4.4.5 Photoallergy or Dermal phototoxicity
- 4.4.6 Rectal Tolerance Test

**4.5 Genotoxicity**

**4.6 Allergenicity/ Hypersensitivity**

**4.7 Carcinogenicity**

**4.8 GLP compliance statement dated 19 Dec 2025 along with certificates – Toxicology studies**

**MODULE IV B: ANIMAL PHARMACOLOGY DATA**

**5.1 Summary**

**5.2 Specific Pharmacological Actions**

**5.3 General Pharmacological Actions**

**5.4 Follow up and Supplemental Safety Pharmacology Studies**

**5.5 Pharmacokinetics: Absorption, Distribution, Metabolism, Excretion**

**MODULE V: CLINICAL DATA**

**6.1 Human/ Clinical Pharmacology (Phase I) Data**

- 6.1.1 Summary
- 6.1.2 Specific Pharmacological Effects
- 6.1.3 General Pharmacological Effects
- 6.1.4 Pharmacokinetics: Absorption, Distribution, Metabolism, Excretion
- 6.1.5 Pharmacodynamics/ Early Measurement of Drug Activity
- 6.1.6 Study Reports Protocol Number: KER-050-01 dated 10 Sep 2021

**6.2 Therapeutic Exploratory Trials (Phase II) Data**

- 6.2.1 Summary
- 6.2.2 Study Reports – Phase II

**6.3 Therapeutic Confirmatory Trials (Phase III)**

- 6.3.1 Summary
- 6.3.2 Individual Study Report
- 6.3.3 Study Reports

**6.4 Special Studies**

- 6.4.1 Summary
- 6.4.2 Bioavailability/ Bi-Equivalence

**6.5 Other Studies**

- 6.5.1 Geriatric study
- 6.5.2 Pediatrics
- 6.5.3 Pregnant or Nursing Women

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## **MODULE VI: CLINICAL TRIAL RELATED DOCUMENTS**

7.1 Study Protocol No. TAK-226-3001 Original Protocol dated 01 Sep 2025

7.1.1 Declaration that as per protocol, whether the patients will receive the Standard of Care dated 19 Dec 2025

7.2 Patient Information Sheet (PIS) and Informed Consent Forms (ICFs) as the Table 3 of Third Schedule of New Drugs and Clinical Trial Rules 2019 and Patient Materials:

### **Materials: Informed Consent Forms (ICFs):**

- TAK-226-3001 Master India Participant Information Sheet and Consent Form Version 1.0 20Jan2026
- Master India Pregnant Partner Authorization for Pregnancy Follow-up 1.0 20Jan2026
- Other\_V9.0IND(en)1.0(20Jan2026)
- Audio Visual (A-V) Recording Declaration\_V6.0IND(en)1.0(17Oct2025)

### **Patient Materials:**

- Participant ID Card, 11 Nov 2025 [V01 IND(en)01]
- Paper COAs for TAK-226-3001 – English (India)
- ELRISE MDS\_Self-Administration Diary Card\_V2.0\_31DEC2025\_IN\_EN
- ELRISE MDS\_Self-Administration Instructions to Patients\_V1.0\_31DEC2025\_IN\_EN

7.3 Undertaking to provide medical management and compensation in case of clinical trial related injury or death

- Undertaking from Sponsor dated 19 Dec 2025
- Undertaking from Applicant (IQVIA RDS (India) Pvt. Ltd.) dated 04 Feb 2026

7.4 Declaration regarding financial status of the applicant vis-à-vis Medical Management and compensation to be paid to the trial participants (in case of injury or death in clinical trial)

7.5 Subject Case Report Form Version 1.1 generated on 17 Oct 2025

7.6 Investigator's Brochure for Elritercept (TAK-226) Edition 8 dated 01 Jul 2025

7.6.1 Affidavit declaring that the information about study drug as mentioned in Investigator's Brochure is Authentic and based on sponsor's own research dated 18 Dec 2025

7.7 List of Participating Sites with Principal Investigators and EC details

7.7.1 India Specific CTA template

7.7.2 Undertaking by the Investigators as per Table 3 of Third Schedule of New Drugs and Clinical Trial Rules 2019, including List of Investigators with qualification along with CV, MRC, GCP certificate and EC registration certificate

7.7.3 Ethics Committee Approval

7.8 Proposed IMP Labels for India

7.9 Insurance certificate dated 19 Jan 2026

7.10 Assessment of risk versus benefit to the patient (for this proposal)

7.11 Innovations vis-a-vis Existing Therapeutic option (w.r.t this proposal)

7.12 Unmet Medical Need in the Country (of IMP/Trial proposal)

7.13 Publication statement from sponsor

7.14 Post Marketing (Phase IV) Studies

7.14.1 Patent and Marketing status of Drug in India and other countries dated 16 Dec 2025

7.14.2 Product Prescribing Information

7.14.3 Summary of Phase I, Phase II & Phase III Studies

7.15 Any other information (optional) - Pharmacy\_Manual\_V2\_Global\_Final\_12DEC2025