Pharmacokinetics, Pharmacodynamics, and Safety of Single and Multiple Oral Doses of Vadadustat in Healthy Japanese and Caucasian Subjects

Gurudutt A. Chandorkar,1 Stanford Jhee,2 David Han,1 Kara Schmelzer,1 Molly Sherman,1 Karishma Manzur,1 Amit Sharma,1 Qing Zuraw,1 Emil deGoma1

1Akebia Therapeutics, Inc., Cambridge, MA; 2PAREXEL International Early Phase, Glendale, CA; 3California Clinical Trials Medical Group in affiliation with PAREXEL Early Phase, Glendale, CA

Introduction

Vadadustat (NOX0160) is an orally delivered, multiple-domain Factor alpha inhibitory protein (FAP) prodrug candidate in Phase II development for the treatment of anemia in patients with renal dysfunction.

In a randomized, double-blind, placebo-controlled, multiple-ascending dose study to assess the pharmacokinetics, pharmacodynamics, and safety of oral vadadustat in healthy Japanese and Caucasian adults, serum erythropoietin (EPO) levels were increased significantly in a dose-dependent manner following single and multiple doses of vadadustat, suggesting that oral vadadustat preserved the normal diurnal pattern of EPO secretion and maintained serum EPO levels within the physiologic range.

In completed Phase 1 and Phase 2 studies, vadadustat demonstrated dose-proportional pharmacokinetics (PK) and pharmacodynamics (PD), and achieved akinesic, physiologically-meaningful increases in serum erythropoietin (EPO) in healthy volunteers.

The ongoing Phase 3 PRO-SID study will assess the efficacy and safety of vadadustat compared with darbepoetin alfa in patients with renal dysfunction.

Demographics and Baseline Characteristics

Demographics and baseline characteristics were generally balanced between Japanese and Caucasian subjects across treatments.

All 48 subjects enrolled in the trial completed the study and were included in the PK, PD, and safety analyses.

Study Design

• Randomized, double-blinded, placebo-controlled, multiple-ascending dose study in healthy (EF, PD, safety and tolerability) and anemic (EPO, PK/PD) Japanese and Caucasian adults

Eligibility Criteria

• Race: Japanese, Caucasian
• Gender: Male
• Age: 20–55 years old
• Body weight: 50–110 kg
• BMI: 18–30 kg/m²
• Healthy adult male
• Age: 20–55 years old
• Body weight: 
• No deaths or serious AEs were reported during the study

PK/PD Summary

• Dose-dependent increases in serum EPO concentrations in Japanese and Caucasian subjects were observed across dose levels following single and multiple doses of 100, 300, and 600 mg EPO dose daily, the effect was greater in Japanese than in Caucasian subjects.

Safety

• No deaths or serious AEs were reported in any Japanese subject following either single or multiple vadadustat doses
• Administration of vadadustat preserved the normal diurnal pattern of EPO secretion and maintained serum EPO levels within the physiologic range
• There were no meaningful differences in serum EPO concentrations in healthy Japanese and Caucasian subjects administered single and multiple vadadustat daily doses
• Vadadustat was well-tolerated in healthy Japanese and Caucasian adults

Results

• Serum EPO concentrations in Japanese subjects at the 600 mg dose were slightly higher than in Caucasian subjects across treatments
• Administration of vadadustat preserved the normal diurnal pattern of EPO secretion and maintained serum EPO levels within the physiologic range
• There were no meaningful differences in serum EPO concentrations in healthy Japanese and Caucasian subjects administered single and multiple vadadustat daily doses
• Vadadustat was well-tolerated in healthy Japanese and Caucasian adults

Conclusions

• The study demonstrated that vadadustat exposure was similar in healthy Japanese and Caucasian subjects administered single and multiple vadadustat daily doses
• There were no meaningful differences in serum EPO concentrations between healthy Japanese and Caucasian subjects administered single and multiple vadadustat daily doses
• Vadadustat was well-tolerated in healthy Japanese and Caucasian adults

• The study's positive results in healthy Japanese and Caucasian subjects support continued development of vadadustat in healthy subjects administered single and multiple vadadustat daily doses

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References


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