Introduction

• GSK1278863A is a novel small molecule that has demonstrated in vitro and in vivo inhibition of the hypoxia-inducible factor (HIF) prolyl hydroxylases EGLN1/3. GSK1278863A increased erythropoietin (EPO) and Hb production following repeat oral administration to preclinical species; EPO increased following single dose oral administration to humans.

• Study PX111427 was a single-blind, randomized, placebo controlled (active-placebo ratio of 2:1), dose-rising, single oral dose (2 to 300 mg), sequential parallel group study to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy adults (ClinicalTrials.gov, reference NCT00750256).

• PK: GSK1278863A PK were linear with dose proportionate increases in plasma exposure; \( t_{\text{max}} \) ranged between 1.25-2.00 h and 1.12-2.00 h from 0.8-4.0 mg/kg.

• PD: Significant increases in circulating plasma EPO were observed following single-dose administration of 15, 50, 150, and 300 mg of GSK1278863A (Figure 1).

Objectives

An exploratory research collaboration utilizing the Hematopoiesis PhysioLab® incorporating GSK1278863A’s mechanism of action was established and simulations were conducted to predict changes in Hb under various scenarios and compared to a standard recombinant erythropoietin (rEPO) regimen in healthy subjects and patients with kidney disease.

Methods

• Simulations were carried out in the Entelos Hematopoiesis PhysioLab platform which is a large-scale, ordinary differential equations (ODEs) based model that captures key aspects of the hematopoietic physiology.

• Public literature data 1-4 was used to model HIF regulated production of EPO. Single-dose PK/PD data was used to establish a two-compartment PK model of prolyl hydroxylase inhibition (PHI), and to represent GSK1278863A effect on HIF regulation of EPO production (Figures 2 and 3).

Results

• In virtual healthy subjects, 25 mg QD would achieve the desired increase in Hb, while doses >50 mg QD may result in Hb increasing >1g/dL over 2 wks especially in high responders (Figure 5).

• EPO production in response to a GD or BD dosing to virtual healthy subjects predicted Hb response approached steady-state after 14 days (Figure 6).

• As displayed in Figures 6 and 7, the simulation of clinical response of a wide array of virtual patient phenotypes for a range of doses and dosing schedules facilitated exploration of various study designs, and optimization of inclusion criteria (i.e., baseline severity, Hb, dose and dose titration, and safety criteria (i.e., \( Hb > 13g/dL \) or \( >1g/dL \) over 2 wks in a given patient phenotype; predicted duration of Hb return to baseline once dose suspended).

• Predicted average VEGF (C24) following GSK1178863A 25 mg QD was 19-54 pg/mL and dependent on drug responder type.

Conclusions

• Simulations revealed a heterogeneous GSK1278863A response and emphasized the importance of patient stratification and an adaptive approach for Phase 2 designs.

• Understanding the predicted response of a wide array of diverse CKD phenotypes to a range of GSK1278863A doses + dose durations can help optimize the inclusion criteria and dosing regimen.

• Further modeling with additional healthy subject and patient data could help refine the clinical trial design by employing a prevalence-weighted population of CKD patients and exploring dose titration strategies.

• Exploration of GSK1278863A’s effects in Stage 5 (dialysis) CKD patients may provide additional confidence in forecasting the potential response in this population.

References


