[F159] A TISSUE DISTRIBUTION STUDY OF ^{14}C-PEGINESATIDE FOLLOWING INTRAVENOUS ADMINISTRATION IN MALE CYNOMOLGUS MONKEYS USING QUANTITATIVE WHOLE-BODY AUTORADIOGRAPHY (QWBA) AND MICROAUTORADIOGRAPHY (MARG)

Kathryn Woodburn,[1] Christopher Holmes,[1] Kei-Lai Fong,[2] Steven Sloneker,[3] Paul Strzemienski,[4] Eric Solon[5]. [1]Affymax Inc, Palo Alto, CA, USA; [2]Accellient Partners, LLC, Berkeley, CA, USA; [3]Calvert Laboratories Inc, Scott Township, Pa, USA; [4]QPS, Newark, DE, USA

INTRODUCTION AND AIMS:

Hematide™/peginesatide is a PEGylated, investigational, peptide-based erythropoiesis stimulating agent (ESA). It was designed and engineered to stimulate specifically the erythropoietin receptor (EPOr), yet it has no sequence homology to rHuEPO. Peginesatide is currently in clinical development for the treatment of anemia associated with chronic renal failure. This study was designed to determine the erythropoietic response, pharmacokinetics, tissue distribution, and major routes of elimination of ^{14}C-peginesatide following a single intravenous (IV) dose in non-human primates.

METHODS:

Four male Cynomolgus monkeys were administered 2.1 mg/kg ^{14}C-peginesatide IV and sacrificed at 48 hours for MARG analysis or at 1 or 3 weeks for QWBA analyses. Blood samples were collected at various times for pharmacokinetic and hematologic analyses. Total radioactivity in whole blood and plasma PK samples was determined by combustion/liquid scintillation counting (LSC) analyses.

RESULTS:

^{14}C-peginesatide-induced erythropoiesis was characterized by initial increases in reticulocytes and subsequent time-dependent increases in red blood cell (RBC) parameters, such as hemoglobin (Hgb). At 2 weeks, Hgb was 15.8 g/dL, a 1.9 g/dL increase over the pre-dose level. Pharmacokinetics were characterized by low clearance (0.885 and 0.520 mL/kg/h for blood and plasma, respectively) and a prolonged half-life (69.8 and 70.9 hours in blood and plasma, respectively). Radioactivity concentration was greater in plasma than blood, indicating minimal association with blood cells. QWBA C_{max} values were generally observed at 48 hours post-dose, with the distribution likely reflecting sustained blood levels of peginesatide and confinement of test article to the vasculature with slow distribution into the tissue. At 1 week post-dose, radioactivity concentrations were decreasing in most tissues except the spleen, lymph node, bone marrow, adrenal gland (sites containing EPOr), and urine, where their increase suggested a partitioning of peginesatide or cummulated excretion (urine). Concentrations increased through 3 weeks for the spleen and lymph node and pronounced levels persisted in the bone marrow and adrenal gland. MARG analysis at 48 hours post-dose revealed distribution of radioactivity in the bone marrow, renal cortex (glomeruli, associated ducts, interstitial cells), and liver.

CONCLUSIONS:

^{14}C-peginesatide administration to Cynomolgus monkeys resulted in pronounced erythropoiesis with pharmacokinetics characterized by low clearance and a prolonged half-life. Renal excretion was a primary route of elimination. Pronounced levels persisted in the bone marrow (hematopoietic target site) through 3 weeks, indicating prolonged, selective localization of peginesatide to known hematopoietic/EPOr sites in non-human primates.

DISCLOSURE:

Kathryn Woodburn and Christopher Holmes are employees of Affymax. Affymax is developing peginesatide for the treatment of chronic renal failure in dialysis.

Date: Friday, June 24, 2011
Session Info: Poster Session: Anaemia in CKD 1-5

Close Window