

Discussion

[0045] The cGMP-manufactured α -artesunic acid parenteral dosage form of the invention offers several advantages over current, commercially available version(s) of Artesunate drug.

[0046] 1. The cGMP-manufactured sterile dissolution medium, a 0.30 M, pH 8.0 solution of sodium phosphate, completely dissolves the α -artesunic acid in 2-3 min, requiring only gentle swirling. This rate of dissolution is several fold faster than that found for the Guilin product, following its directions for preparation given in its package insert.

[0047] 2. Because the dissolution of AS in phosphate is not accompanied by gaseous evolution, as in the case where bicarbonate is used, determining solution completeness is readily achieved.

[0048] 3. The solution prepared in phosphate is ready for administration, as no further preparation is required. The Guilin product, on the other hand, requires an additional step of dilution of the AS/bicarbonate solution with 5 mL of 5% glucose, which also must be sterile.

[0049] 4. The pH of our 10 mg AS/mL solution in phosphate is 7.2, whereas that for 10 mg AS/mL solution in bicarbonate/glucose is 7.9, a solution pH that is higher than ideal for parenteral administration.

[0050] 5. The osmolality of our 10 mg AS/mL solution in phosphate is 320 and that for the 10 mg AS/mL solution in bicarbonate/glucose is 410, a value also higher than ideal for parenteral administration.

[0051] 6. The phosphate buffer solution of the GMP manufactured formulation allows AS concentrations high enough for effective IM treatment.

[0052] Although hydrolysis of AS in phosphate or bicarbonate/glucose begins almost immediately upon dissolution, the rates of decomposition in the two media are comparable. After two hrs at -24° C. the solutions were still visibly clear and therefore still can be administered.

[0053] In keeping with US FDA requirements, vials of the phosphate vehicle, the AS, and the placebo are undergoing accelerated and shelf-life stability studies.

Efficacy in Trials:

[0054] An Investigational New Drug Application (IND-64769) on this drug product has been filed with the FDA and has been approved for use in clinical trials. Phase Ia Safety and Tolerance single dose clinical trials have been concluded and were successful.

[0055] Phase Ia Safety and Tolerance of GMP Formulation

[0056] Phase Ia is a single dose double-blind placebo-controlled, randomized study to evaluate the safety and tolerance of the GMP formulation of intravenous artesunate. The study has been completed successfully as is necessary to proceed to Phase Ib and Phase II trials. Phase Ib and Phase II trials are in progress.

[0057] Phase Ib Safety, Tolerance and Pharmacokinetics/Pharmacodynamics of GMP Formulation

[0058] A Phase Ib is a double-blind, placebo-controlled, randomized multiple dose escalation study to evaluate the safety, tolerance, and pharmacokinetics/pharmacodynamics of GMP formulation of intravenous artesunate in healthy human subjects in 3 doses using a dose escalation format using a placebo control. An objective is to determine the safety of multiple dose administration of escalating doses of

artesunate that bracket the anticipated compassionate use dose of 2.4 mg/kg by measuring adverse events (AE) and cardiovascular responses (heart rate (HR), blood pressure (BP), and electrocardiogram (ECG)). Another objective is to determine the safety and tolerability of the compassionate use of 3 doses of artesunate in escalating doses of 0.5, 1.0, 2.0, 4.0, and 8.0 mg/kg with placebo control. The primary and secondary outcomes are to assess AE and hemodynamic and cardiac responses (BP,HR, ECG) and to determine pharmacokinetic parameters of artesunate and its major metabolite DHA as well as to assess preliminary dose-toxic response.

[0059] The study design is as follows: Phase I, randomized, double-blind, placebo-controlled trial using multiple ascending doses of intravenous artesunate to determine its safety, tolerability and pharmacokinetics in healthy male and female subjects. Subjects will be screened within 21 days of dosing. At the screening visit, subjects will undergo baseline VS, PE, CBC with smear, differential and indices, reticulocyte count measured by flow cytometry, haptoglobin, COAGs, Chem, UA, urine drug screen, urine HCG and medical and medication history. Eligible subjects will be scheduled for a 6-hour outpatient visit for pre-dose ECGs and VS done to approximately match dosing schedule on Day 1. On Day 0, subjects will be admitted to the CPU to begin the inpatient phase of the study. Subjects will have a brief physical and review all procedures for the inpatient stay. On Day 1, pre-dose, VS and ECG will be performed. Subjects then will receive IV study drug or placebo. Subjects will be closely monitored by evaluating hemodynamic measurements, periodic ECGs, and assessment of spontaneously reported AEs. Blood will be drawn for blood count and chemistry analysis within 12 hours of the first and last doses. PK will be drawn at designated times after each dose administered. On Days 2 and 3 subjects will receive their second and third doses, respectively, of study drug or placebo followed by close clinical monitoring and laboratory measurements as described for the first doses given. Subjects will be discharged 24 hours after the third dose of drug or placebo and followed as outpatients on Days 7, 10, and 15. The study population will consist of 40 healthy male and non-pregnant female adults given artesunate GMP manufactured for injection intravenously.

[0060] The duration of the study will be a screening of up to 21 days; 5 days (four nights) inpatient and 3 outpatient visits (last visit day 15) per patient.

[0061] Phase II Trials:

[0062] In Phase II trials, the artesunic acid parenteral dosage form of the invention was given intravenously to human subjects in Africa to treat malaria. In trials in Africa, COL Peter Weina, Chief, Department of Pharmacology, Walter Reed Army Institute of Research has reported 30 adult male and female volunteer patients with uncomplicated malaria have been successfully treated using the treatment regimen as outlined in this application. Successfully treated is defined as safely clearing *P. falciparum* malaria parasites from the blood. Patients were given a single dose of 1-4 milligrams per kilogram body weight in the form of an injection through an IV catheter (a tube with a needle attached) once a day for 3 days in a row. There were no adverse effects from the GMP IV treatment of the artesunate of the invention. The single adverse effect was with the standard-of-care positive control drug Malarone.

Stability Studies

[0063] Six thousand dry-filled vials of formulated artesunate for clinical use have been packaged. One thousand of the