TITLE OF THE STUDY: Evaluation of Iron Species in Healthy Subjects Treated With Generic and Reference Sodium Ferric Gluconate

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Abbreviated title: IV Iron Safety: Evaluation of Iron Species in Healthy Subjects

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PROTOCOL SUMMARY

TITLE OF THE STUDY: Evaluation of Iron Species in Healthy Subjects Treated With Generic and Reference Sodium Ferric Gluconate

PHASE: Phase 4

METHODOLOGY: Randomized, open-label, 2-way, cross-over, two period, fasted single-dose study comparing plasma profiles of brand and generic products

STUDY CENTER: University of Maryland

NUMBER OF SUBJECTS: n=44

STUDY OBJECTIVES: The primary outcome will be the assessment of non-inferiority of the generic colloid product against the reference colloid product with respect to non-transferrin bound iron (NTBI), after single-dose i.v. administration of brand and generic sodium ferric gluconate injections in n=44 healthy subjects. NTBI will be characterized by Drug Bound Iron (DBI). Secondary outcomes include plasma Total Iron and Transferrin Bound Iron.

Evaluation of Iron Species in Healthy Subjects Treated With Generic and Reference Sodium Ferric Gluconate

Lay Summary

An approved treatment for anemia or low blood count due to chronic kidney disease is IV (intravenous, given into the vein) injection of an iron treatment. IV iron increases iron in the blood. Many IV iron therapies are now available in both brand name and generic forms. One common IV iron product is sodium ferric gluconate (SFG) sold as brand name Ferrlecit. Ferrlecit has recently become available in generic form and has come under some scrutiny for whether the generic is comparable in safety to the brand name form. The purpose of this research project is to see if the brand and generic IV iron products produce the same amount of iron in the blood in healthy volunteers, including an iron form that more toxic than other iron forms.

Background

IV iron is a complex colloidal product. In 2011, a 'Reflections Paper on Non-Clinical Studies for Generic Nanoparticle Iron Medicinal Product Applications' was published by the European Medicines Agency. In this paper, the European Medicines Agency cautioned that the approach currently employed for characterizing small molecule generic products is not adequate for characterizing iron colloidal complexes. The group cautioned that the physiochemical properties of the iron colloid products can differ significantly based upon the mean/median size and distribution of the product. As a result, they posited that generic preparations be characterized in more detail to ensure that their physiochemical properties are comparable to brand. For iron-based complexes, it was recommended that in vivo comparative studies be performed.

Procedures

There will be a screening visit and two pharmacokinetic study visits for all enrolled subjects. Subjects will be enrolled on an ongoing basis until either the anticipated number of required subjects for n=44 completed subjects is achieved, or until n=120 is achieved. In each pharmacokinetic study visit occasion, individual subjects will receive a single dose of one (and only one) of two drug products. The products are brand IV sodium ferric gluconate and generic IV sodium ferric gluconate.

Subjects will be randomized into one of two sequences, R or T. Sequence R will receive drug products in the following order of: reference (i.e. brand) then test (i.e. generic). Sequence T will receive drug products in the following order of: test (i.e. generic) then reference (i.e. brand). Randomization is to a sequence R or T.

In each administration, product will be administered undiluted as a slow intravenous injection dose of 125 mg over 10 minutes, with at least a 28 day washout period. In each period, blood samples will be collected 0-36 h.

Screening: At this visit, the HIPAA and consent forms will be reviewed with the subject by a member of the research staff; they will be signed and dated. Consenting will also discuss and provide a payment plan. Demographic information will be obtained. A brief physical exam with a medical/medication history, including smoking and alcohol, will be conducted. Clinical safety labs at screening of serum chemistries include hepatic and renal function tests (i.e. creatinine, BUN, AST, ALT, and total bilirubin), serum ferritin, as well as hemoglobin to test for anemia. Female subjects will be asked if they are breast feeding, trying to become pregnant, or are pregnant. Female subjects of child-bearing potential will have a urine pregnancy test. The subject will be asked about willingness to avoid caffeine products for 24 hours before and day of study visit. The subject will be asked about willingness to stop Over-the-Counter (OTC) drugs for 24 hours before and days of study visits. The subject will be asked if willing to fast during the study visits except for meals supplied in the study. If subject meets all eligibility requirements, then appointments are scheduled for the drug study visits. The first study visit will be within 30 days of the screening visit.

Drug/Pharmacokinetic Study Visits: Subjects will be requested to arrive by approximately 6:30am on study visit, after an overnight fast of 10 hours prior to taking test drug, and remain fasted for an additional 4 hours. Women of child-bearing potential will take a urine pregnancy test. Study test drug will be intravenously administered over 10 minutes at approximately 7am. Blood samples will be collected at 0 min (i.e. immediately prior to start of infusion) and at 10, 20, and 40 min and 1, 2, 3, 4, 8, 12, 16, 24, and 36 h after the start of the infusion. Standardized meals and snacks (including with respect to iron) will be served during each 36 hour stay. Meals and snacks include beverages.

A lunch will be served four hours after taking test drug (i.e. immediately after 4 hr blood draw), or approximately 11am. An afternoon snack will be served 4 hours later (i.e. immediately after 8 hr blood draw), or at approximately 3pm. Dinner will be served 4 hours later (i.e. immediately after 12 hr blood draw), or at approximately 7pm. An evening snack will be served 4 hours later (i.e. immediately after 16 hr blood draw), or at approximately 11pm. Breakfast will be served 8 hours later (i.e. immediately after 24 hr blood draw), or at approximately 7am. Lunch and an afternoon snack will be served 4 hours later (about 11am) and 8 hours later (about 3pm),

respectively. Subjects will fast between meals or snacks except for water. No water is allowed 1 hour before or 1 hour after start of drug infusion. Subjects will return for the next

drug/pharmacokinetic study visit, preferably 4 week later with a minimum of a wash out of 28 days.

Subjects will be monitored for AEs during study days, including hypersensitivity, hypertension, and hypotension. Study physician will be present at the start of iron infusion and until at least 30 min. At each study visit, subjects will be asked about any AE that may have occurred between study visits. A phone follow-up will be attempted about 7 days after last visit to inquire about well-being of study participants and any AEs. All AE will be documented in the source documents by research personnel.

AEs and SAEs will be reported per UMB HRPO guidelines.

INCLUSION CRITERIA:

1 Males or female, with age 18-65 years old, systolic blood pressure within 90-150 mmHg, and diastolic blood pressure within 60-90 mmHg

2 Healthy volunteers: Subjects in good health including being iron replete and not anemic, as determined by screening evaluation that is not greater than 30 days before the first drug study visit

3 Willing to avoid caffeine containing products 24 hours prior to and day of study visits

4 Willing to stop all OTC medications for 24 hours prior to and during study visits

5 Able to provide informed consent

6 Weight at least 55 kg

EXCLUSION CRITERIA:

1 Presence of significant medical disease (including cardiovascular, pulmonary, hematologic, endocrine, immunologic, neurologic, gastrointestinal or psychiatric)

2 Subjects who are iron deficient or with iron overload

3 Presence of hepatic or renal disease

4 Pregnant women, breast feeding or trying to become pregnant

5 Excessive alcohol use (i.e. current physical, behavioral, or personal manifestations related to the abuse or dependency on alcohol)

6 Routine use (i.e. daily or weekly) prescription medication except birth control pills

7 Currently taking iron in any form (e.g. oral or IV)

8 Allergic to IV iron, including sodium ferric gluconate, or any of its inactive components, including benzyl alcohol

9 Undergoing therapy for solid tumor or blood malignancy

10 Any condition in which in the opinion of the PI or medical physician would increase risk to the subject or interfere with the integrity of the study

11 Donated blood within last 56 days of screening. Received IV iron or RBC transfusion(s) 10 days prior to screening. Plan to donate blood, or receive IV iron or RBC transfusion(s), during the study period.

12 Anticipated need for surgery requiring general anesthesia 30 days prior to screening or during the study period.

Monitoring Plan

Data Safety Monitoring will be performed by a physician who Is not on the study team and who routinely prescribes intravenous iron in their practice. In closed review of subjects (i.e. de-identified data), the physician will review the following information: AEs (recorded on a flow sheet), screen failures, subject withdraws and terminations, and enrollment. Reviewed data will include clinical summaries, enrollment numbers, and adverse events. Additionally, she will conduct such reviews after the completion of the first four subjects, and then quarterly.

Statistical Analysis Plan

The primary outcome will be the assessment of non-inferiority of the generic colloid product against the reference colloid product with respect to non-transferrin bound iron (NTBI), after single-dose i.v. administration of brand and generic sodium ferric gluconate injections in n=44 healthy subjects. NTBI will be characterized by Drug Bound Iron (DBI).

The hypothesis is that NTBI exposure from generic is over 1.25-fold greater than the NTBI exposure from brand. The null hypothesis is the NTBI exposure from generic is less than 1.25-

fold greater than the NTBI exposure from brand. This assessment will employ the upper limit of a one-sided 95% confidence interval of generic NTBI area under-the-curve (AUC) and the brand NTBI. The upper limit of this confidence interval will be constructed using ln-transformed AUC values, similar to well developed average bioequivalence testing from 2-way cross-over studies. The one-side 95% confidence interval will be computed using commercial software as the upper bound of the 90% two-sided confidence interval of a two-way crossover study. Secondary outcomes will include plasma Total Iron and Transferrin Bound Iron.