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Title: Pilot study: randomized, placebo-controlled comparator trial of IV vs oral iron treatment of RLS with Iron deficiency anemia. (IVOR-IDA)

Principal Investigator: Michael Auerbach, M.D.

Protocol: IVOR-IDA

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Type of Study: Double-blind comparator of efficacy of oral (ferrous sulfate) vs. Intravenous iron (ferumoxytol) for treatment of the restless legs syndrome (RLS) occurring with iron deficient anemia (IDA)

Supported by: AMAG pharmaceuticals

Summary:

The restless legs syndrome (RLS) (also known as Willis Ekbom Disease) occurs in about 1/3rd of patients with iron deficiency anemia (IDA). Treatment correcting the IDA is expected to also be effective for reducing or eliminating the RLS with IDA. Two accepted treatments for IDA (oral ferrous sulfate, intravenous ferumoxytol) will be compared for efficacy and speed of response for treatment of RLS occurring with IDA (RLS-IDA). In this study 70 RLS-IDA patients will be randomly assigned 35 each to oral or IV iron treatment using double-blind procedures. Primary outcome will be determined at 6 weeks of treatment with a follow-up at 12 months after treatment. Non-responders at 6 weeks after treatment may, if they qualify, have an open-label IV iron treatment and they will be followed with the same evaluations used after the first set of IV iron treatments.

Primary objectives

1. Determine relative effect sizes of standard IV and oral iron treatment of RLS with iron deficiency anemia
2. Determine time course of treatment response

Exploratory hypotheses:

1) Primary exploratory hypothesis: Reduction in RLS-IDA severity measured by the CGI-2 (much or very much improved) will be greater for IV than oral iron treatment at 6 weeks after starting treatment.

2) Secondary exploratory hypothesis: there will be a greater change from baseline in the IRLS score assessing severity of RLS for IV than oral iron treated patients.

Introduction

Background:

Low IRON status is associated with RLS: RLS has been documented to have significant decreased iron concentrations in the substantia nigra [1] and other areas [2]. This has been documented in multiple studies using both MRI [2] [3] [1]and ultrasound [4]. Peripheral

iron status also relates to RLS severity [5] and both oral and IV iron treatments significantly reduce RLS symptoms compared to placebo [6, 7].

RLS occurs commonly with iron deficiency anemia: The prevalence of RLS among the IDA patients seen in the Auerbach clinic is 32% for any RLS and 24% for clinically significant RLS [8]. This is about 5 times the 7% prevalence of any RLS in the general population and about 10 times the 2.7% prevalence of clinically significant RLS [9]. Thus RLS with IDA (RLS-IDA) is not only more common and but also more severe than that in the general population.

Standard treatments for IDA also treat RLS without IDA. Both oral and IV iron are considered standard treatments for IDA [10]. These same treatments also reduce RLS symptoms. Oral iron as ferrous sulfate 325mg taken twice a day produced significant reduction in RLS symptoms in a blinded placebo-controlled study [7]. IV iron given as ferric carboxymaltose in 2 doses of 510 mg spaced 5 days apart also reduces RLS symptoms significantly more than placebo [6].

Rationale for study: It is assumed the treatments that reverse the IDA will also reduce the RLS symptoms occurring with IDA. This is supported by these treatments benefitting RLS patients without IDA. But this has never been demonstrated in a prospective controlled trial. The iron stores, however, are less in the IDA than general population. The IDA-RLS may therefore require more aggressive iron treatment than is used for RLS without IDA and possibly even more aggressive iron treatment than is usually given for IDA. In particular despite the recovery of anemia after 6 weeks of oral iron treatment, the actual iron stores remain low. In contrast the IV iron treatment at about 1000 mg of iron corrects the anemia and provides a better increase in iron stores over a 6-week period [10]. Thus, if the IDA-RLS results more from the low iron than the anemia it may benefit significantly more from IV than oral iron treatment.

Our major problem in testing the treatment benefits for IDA-RLS for either oral or IV iron is that we do not know the actual effect size of either treatment. We have as an initial estimates the effect sizes from clinical experience with oral and IV iron treatment of IDA-RLS. These have to be considered as provisional estimates of effect sizes. Thus, although we have set the sample size to give adequate power to differentiate iv from oral iron treatment assuming these effect sizes, we do not consider the power estimates to be accurate. We feel they give us an adequate sample to establish effect sizes for future studies and to explore possible differential efficacy for the two treatments. The primary goal of the study is, therefore, to assess effect size. Evaluating differences between the treatments is a tertiary goal of this study.

The decision not to do a placebo control is based on the assumption that the treatment effect size can be adequately determined without a placebo. The decision to do a blinded comparator trial is based on the assumption that we will see differences between the treatments that will establish both the effect sizes and the procedures for a larger study to show these differences. We feel it is very important to determine if efficacy of these treatments differ for RLS-IDA in order to develop guidelines for future treatment of this clinically significant condition affecting many with IDA. We have assumed IV iron will be the preferred treatment for RLS-IDA, but we need to first evaluate this in this pilot study and then in a larger adequately powered clinical study.

Drugs used: The treatment doses are those accepted for treatment of RLS and also appropriate for treatment of RLS-IDA. Choosing doses equivalent to those for the treatment of RLS without IDA will allow a comparison with that literature. We will therefore use for oral iron ferrous sulfate 325 mg taken twice a day matching the dose used in the study of oral iron treatment for RLS without anemia [7]. For IV iron we will use ferumoxytol two doses of 510 mg spaced 2 to 7 days apart. This is the FDA approved dose for treatment of IDA with end stage renal disease. This dose matches the iron dosing used in the study of IV iron treatment for RLS without anemia [6], except we will use ferumoxytol provided by the sponsor rather than ferric carboxymaltose used in the prior trial.

Study Design

The study is a randomized, comparative open label study to evaluate effect size and time course of treatment response for RLS-IAD over 6 weeks with a 46-week follow-up extension. Two medications and placebos will be used with equal random assignment to both groups

- Ferumoxytol intravenous (IV) 1020 mg – 2 vials of 510 mg (IV push, 2-3 mins) each given 2-7 days apart
- Ferrous sulfate 325 mg (oral) tabs morning and evening.
- Placebo: oral vitamin C 500 mg tabs, Saline infusion

Primary outcome is the CGI-2 score at 6 weeks after treatment starts. IV ferumoxytol 1020 mg treatment (2 separate doses 510 mg 2-7 days apart) will be offered to those not significantly responding (CGI-2 scores less than much or very much improved) at 6 weeks after oral-iron treatment and still meeting all requirements for entry to study. All responders will be followed for 12 months after treatment.

Study Objectives

Primary objectives

1. Determine relative effect sizes of standard IV and oral iron treatment of RLS with iron deficiency anemia for the PGI-2/CGI-2 (much and very much improved) and for IRLS scores
2. Determine time course of treatment response for IRLS, PGI-1 and PGI-2 scores

Secondary objectives

1. Estimate survival times for effective treatment (no return to other RLS medications) for 1 year after treatment
2. Evaluate possible predictors of treatment response
   a. Iron status or iron response
   b. IRLS severity
   c. Subject characteristics (age, gender)
   d. Medical factors affecting iron status

Tertiary/exploratory objectives

1. Evaluate significance of efficacy differences if any between oral and IV iron treatments at 6 weeks after treatment: Hierarchical testing first for the percentage with CGI-2 of much or very much improved and second for change from baseline in the IRLS score.
2. Evaluate efficacy benefits of each treatment for usual outcomes related to RLS morbidity: sleep, fatigue, quality of life, and mood.
3. Compare lymphocytes of RLS-IAD and non RLS-IAD for differences in iron related proteins.

Study Procedures

RLS patient ascertainment: A standard patient completed RLS diagnostic questionnaire is given to all of the patients at the Auerbach clinic as part of their routine clinical evaluation not limited to its use in this study. This questionnaire has a sensitivity and specificity of 87% and 94% respectively [11]. The patients identified by the questionnaire as probable RLS will be checked for meeting the inclusion criteria (see below). They will, If they meet criteria, be approached by the research coordinator to consent to this treatment protocol. If they consent then the

coordinator will assign them a protocol number and will obtain any needed blood samples. The coordinator will review the clinical history with the patient to ensure they meet inclusion criteria. If they qualify as determined by inclusion/exclusion criteria (see below) the coordinator will schedule the patient for both a validated telephone diagnostic interview [12] by an RLS specialist at Johns Hopkins and two treatment times to occur 2 – 7 days apart starting after the interview. If the Hopkins interview confirms the RLS diagnosis the treatments will be given as scheduled. If the Hopkins interview does not confirm the diagnosis of RLS the patients participation in this study will end and routine care will be given.

Randomization. A table randomizing assignment of participants in order entered will be used to determine group placement. Once a patient has been confirmed with RLS by the telephone clinical interview they will be given an appointment for IV treatment. At the time of IV treatment the subject will be assigned to either IV or oral iron treatment based on the order in the randomized table. The randomization will be in 7 blocks of 10 with equal treatments in each block. The nursing staff will follow the randomization table based on the order of the subjects tested. Each subject will be assigned a study number at the time of the IV treatment. The subject data will be evaluated using this study number and not the protocol number assigned by the coordinator at the time the patient consented to the study.

Dosing: The patient will receive 2 IV treatments spaced 2 to 6 days apart. These will either be ferumoxytol or placebo. At the time of the first infusion the patient will also be given an opaque bottle, containing either vitamin C tablets or ferrous sulfate 325 mg. The patient is instructed to take each of these pills twice a day for the next 6 weeks. They will be given enough pills to last for 7 weeks with the follow up appointment set for 6 weeks after the first IV treatment.

Blinding: The treatment nurse will determine the assignment the day of the treatment and will complete the appropriate treatment. The research coordinator will not know the patients treatment, will not be present when the patient is being treated and will not have access to files indicating the treatment dose given. During IV treatments the patient will wear eye masks to ensure they do not notice any color differences between the iron and placebo treatments.

Patient visits: There will be 2 to 3 visits at the clinic and telephone contact with the patient at 1,2 and 4 weeks after the start of the IV treatment. During the 12 month follow up there will be 4 more telephone contacts with the patient. (See appendix for schedule of visits.)

Agent and administration for IV iron and placebo

IV iron: The study will use a commercially available preparation of ferumoxytol. Ferumoxytol is currently marketed as an iron replacement product indicated for the treatment of iron defi ciency anemia in adult patients with chronic kidney disease (CKD), and it is FDA-approved for this indication. Ferumoxytol (30 mg/mL) is available for intravenous injection in single use vials. Each vial contains 510 mg of elemental iron in 17 mL. Ferumoxytol can be administered as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec). It is stored at controlled room temperature (20° to 25°C [68° to 77°F]). Excursions are permitted to 15° – 30°C (59° – 86°F). Pre-treatment medications are not required.

In this study 501 mg of ferumoxytol (one vial) will be diluted in 100 ml normal saline and administered with an infusion pump over a 15- minute period.

Patients will have vital signs measured and recorded immediately prior to drug administration and will be observed in the clinic for 60 minutes following completion of the infusion with frequent determination of vital signs and ascertainment of signs or symptoms of adverse effects

Placebo: Normal Saline will be administered following exactly the same procedure as that for IV iron.

Agent and administration for oral iron and placebo
Oral iron: This study will use Ferrous sulfate 325 mg tablets. The medication is to be taken together twice a day. If signifiant stomach distress occurs the patient may elect to take the medication with food and must then notify the research coordinator. The pills will be provided in opaque bottles with exactly enough for 7 weeks and a pill count will be made at the 6-week follow up to determine compliance. The oral pills will be stopped at the 6-week evaluation time.

Placebo: Standard vitamin C 250mg, given in the same bottle as the oral iron.

Subject schedule**:** (See appendix for chart of visits)
There will be 2 – 3 visits at the Auerbach clinic and telephone evaluations conducted by the Hopkins doctors prior to the start of treatment. After the first IV treatment there will be a telephone evaluation at 1, 2 and 4 weeks later and a clinic visit for blood tests at 4 weeks after the first of the pairs of IV treatment and again at about 6 weeks after the first of the pair of IV iron treatments. At 6 weeks after treatment responders will continue in the study with telephone evaluations of their RLS symptoms and medications at about 3, 6, 9 and 12 months after the first IV treatment. At 6 weeks after treatment non-responders will be given the option of receiving the IV ferumoxytol following the same procedure as at the initial treatment with a 6-week period of observation except this will be open label. Both the patient and the coordinator will know that ferumoxytol was given at this repeat dosing. This option will be given only if the patient continues to meet all the inclusion/exclusion criteria for the study noted below, except they will not be excluded for their prior IV treatment in this study. Those receiving the repeat IV dosing at 6 weeks will follow all the same procedures used after the first IV dosing, e.g. telephone safety checks and RLS symptom evaluations at 24-48 hours, 1 week and 4 weeks after initial treatment and a repeat clinic visit at about 6 weeks after the first of the two repeated IV treatment. This 6-week clinic visit will repeat blood tests, adverse event reporting and clinical evaluation of the RLS. The responders to this repeated IV treatment will be followed for up to one year following the same procedures as responders. The non-responders will end the study at this point.

Patients continuing in the one year follow up will be followed for RLS symptoms over the entire year. The telephone evaluation at 12 months after treatment will end the study for these patients Appendix A provides a flow sheet of the subject's schedule.

Subject population

Subjects with diagnosis of RLS and iron deficiency anemia
Inclusion criteria:

1. Aged ≥ 18 years
2. Diagnosis of RLS based on questionnaire and confirmed by Hopkins Telephone Diagnostic Interview conducted by Dr. Allen or Earley
3. Iron deficiency anemia defined as ID either ferritin < 20 mcg/l, Tsat<19%, anemia Hgb< 13 for both males and females.
4. Willingness to use contraceptive to avoid pregnancy: Women have to be surgically sterile , post menopausal or use one of the following contraceptives during the whole study period and after the

study has ended for at least 5 times plasma biological half-life of the investigational medicinal product: intrauterine devices or hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release).

5. Willingness to participate and signing the informed consent form

Exclusion criteria:

A subject will not be eligible for inclusion in this study if they fulfill any of the following criteria:

1. Iron overload or disturbances in utilization of iron (e.g. haemochromatosis and haemosiderosis)
2. Decompensated liver cirrhosis or active hepatitis (ALAT > 3 times upper limit of normal)
3. Serum ferritin > 500 ng/mL or transferrin saturation >40 %
4. Active acute or chronic infections (assessed by clinical judgment that may be indicated by White Blood Cells (WBC) and C-Reactive Protein (CRP) when these are available)
5. Rheumatoid arthritis with symptoms or signs of active inflammation
6. Pregnant and nursing women
7. History of multiple allergies
8. Known hypersensitivity to parenteral or oral iron or any excipients in the drug products
9. Previous IV iron treatment for RLS
10. Other iron treatment or blood transfusion within 4 weeks prior to the screening or treatment visit
11. Planned elective surgery during the study
12. Current (past 4 weeks) use of drugs that treat RLS, e.g. opioids, alpha-2-delta anti-depressants, dopaminergics (dopamine promoters, dopamine antagonists/blockers)

Any other medical condition that, in the opinion of Investigator, may cause the subject to be unsuitable for the completion of the study or place the subject at potential risk from being in the study, e.g. a malignancy, uncontrolled hypertension, unstable ischemic heart disease, or uncontrolled diabetes mellitus

Study Endpoints for each subject

The following are endpoints for each patient in the study :

1. At evaluation in the clinic at about 6 weeks after the first IV iron treatment.

2. Termination of participation because of significant adverse effect from the IV infusion in the hour observed after the infusion.

3. Significant adverse event after starting the iron treatment and before the 6 week follow-up evaluation that was judged to require ending the study.

4. Subject decision not to continue in the study after the treatment and before the final evaluation.

5. Dr. Auerbach decision that it would be harmful to the patient to continue in the study.

6. Patient is non-compliant with study requirements and Dr. Auerbach judges this non-compliance is enough to significantly alter evaluation of the treatment. (Note that stopping the

oral medication because of intolerance to the treatment is not considered non-compliance, but rather an outcome for the study. Patients discontinuing oral medication for adverse effects may qualify for repeat IV treatment .)

Duration of subject participation:

Participation will continue for 6 weeks after treatment for the primary study and for 12 months after treatment for the extension study for those responding to the initial treatments or the open label repeated IV treatment.

Early termination of study:

Subjects may terminate the study at any time or maybe terminated from the study for non-compliance or if continuation in the study is judged by Dr. Auerbach to be harmful to the patient. A telephone evaluation will be scheduled when possible at the time of early termination. The reason for the early termination will be noted.

Blood tests obtained:

Iron panel, hemoglobin and hematocrit will be obtained from morning fasting venous samples at screening prior to treatment and at 4 and 6 weeks after the first treatment. About 15 ml of blood will be obtained for these tests

An additional 24 ml of blood will be collected for lymphocytes the day of the first IV treatment before the treatment and again at 6 weeks after the treatment.

The iron panel will include serum iron, ferritin, transferrin saturation and total iron binding capacity.

Blood samples will routinely be obtained at Dr. Auerbach's office, but in special cases may be arranged through a remote office, e.g. Quest.

RLS clinical evaluations obtained:

The primary clinical evaluations will be the clinician global rating of improvement (CGI-2), patient global rating of RLS severity (PGI-1) and the international RLS severity scale (IRLS). These will be obtained at each clinic visit and at each telephone evaluation, except CGI-2 will only be obtained after the treatment.

The secondary clinical evaluations will be the MOS sleep scale [13], Fatigue severity scale [14], SF36 short form [15] and the Hospital anxiety and depression scale (HADS) [16]. These will be obtained at baseline and then again at the 6 week post IV clinic evaluation.

Concomitant treatment/medication

ESA, anti-histamines, drugs that treat RLS, dopaminergic treatment and iron drugs beside study drugs are not allowed during the study period

Safety and adverse events

<u>Expected possible adverse events (AE)</u>

Across three randomized clinical a total of 605 patients were exposed to two injections of 510 mg of ferumoxytol [17-19]. Most patients received their second ferumoxytol injection 3 to 8 days after the first injection. Adverse reactions related to ferumoxytol and reported by ≥ 1% of ferumoxytol-treated patients in the randomized clinical trials are listed in the table below. Diarrhea (4.0%), constipation (2.1%) and hypertension (1.0%) have also been reported in ferumoxytol-treated patients. In clinical trials, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 ferumoxytol-treated patients included hypotension, infusion

site swelling, increased serum ferritin level, chest pain, diarrhea, dizziness, ecchymosis, pruritus, chronic renal failure, and urticaria.

Adverse Reactions	Ferumoxytol 2 × 510 mg elemental iron (n=605)
Nausea	3.1%
Dizziness	2.6%
Hypotension	2.5%
Peripheral Edema	2.0%
Headache	1.8%
Edema	1.5%
Vomiting	1.5%
Abdominal Pain	1.3%
Chest Pain	1.3%
Cough	1.3%
Pruritus	1.2%
Pyrexia	1.0%
Back pain	1.0%
Muscle spasm	1.0%
Dyspnea	1.0%
Rash	1.0%

In addition oral iron can cause constipation, diarrhea, stomach cramps and upset stomach. The occurrence of these adverse events noted above for oral iron or ferumoxytol will be specifically recorded at each clinic visit following IV treatment and at the 1 , 2, and 4 week telephone evaluation after the start of the IV treatment.

In the event a patient develops a hypersensitivity reaction during treatment, the patient will receive standard recommended treatment and may not continue in the study.

Definition of Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

- Is fatal
- Is life threatening (places the patient at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Met other significant medical hazard

An AE necessitating hospitalization meets the regulatory definition for “serious” if the in-patient hospital admission includes a minimum of an overnight stay in a health care facility. Any AE that does not meet 1 of the definitions of serious (e.g. an AE requiring an emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the Investigator to meet the “other significant medical hazard” criterion for classification as an SAE. Examples include allergic bronchospasm, convulsions, and blood dyscrasia.

If the above interventions are performed as standard of care and not associated with an AE, the health issue for which the intervention is being performed will not be considered an SAE. If there

is a complication as a result of the procedure and the complication meets at least 1 serious criterion, that complication would be reported as an SAE

Definition of an Adverse Drug Reaction
An ADR is an AE that is judged by the Investigator to be “related” or “possible related” to the study drug (see classification of relatedness below).
In the event a patient develops a hypersensitivity reaction during treatment, the patient will receive standard recommended treatment and may not continue in the study.

Adverse Event Reporting:
Patients will be queried for occurrence of adverse effects following discharge from the clinic by means of follow up by telephone by the study coordinator at 24 hours and 1 and 4 weeks after administration of ferumoxytol. They will also be queried about adverse effects of the treatment at the 6 week follow up meeting. If they continue in the study for the 1-year follow-up they will be asked about adverse effects with each efficacy evaluation conducted by telephone. Adverse events will be recorded and evaluated for relatedness, severity, seriousness, and expectedness. They will be followed-up and reported according to current standards.

The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by the subject are properly collected and recorded in the subject’s medical record as well as in the AE pages of the data forms for this project.

An AE should be described in the following manner: The nature of the event will be described in precise, standard medical terminology (i.e. not necessarily the exact words used by the subject). If known, a specific diagnosis should be stated. Furthermore the Investigator should describe an AE regarding severity, relatedness, action taken, and outcome.
Severity

- Mild: The AE does not interfere in a significant manner with the subject’s normal functioning level, but may be an annoyance
- Moderate: The AE produces some impairment of functioning but is not hazardous to health, but is uncomfortable and/or an embarrassment
- Severe: The AE produces significant impairment of functioning or incapacitation and is a hazard to the subject

Relatedness

- Related: The AE is related to the medicinal product
- Possible related: A causal relationship is conceivable and cannot be dismissed
- Unlikely related: The event is most likely related to an etiology other than the medicinal product
- Not related: No relatedness to the medicinal product

The categories "related" and "possible related" will be classified as related AEs and the categories "unlikely related" and "not related" will be classified as unrelated AEs for the final data review.

Outcome

- Recovered/resolved: Complete clinical recovery without any sequel attributable to the event as per Investigator’s discretion

- Recovered/resolved with sequelae: Complete clinical recovery but with one or more sequels attributable to the event as per Investigator's discretion
- Recovering/resolving: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the study
- Not recovered/not resolved: The subject's condition has not improved and the symptoms are unchanged
- Fatal
- Unknown: The subject's condition is unknown. This term should only be used when no other definition is possible e.g. the subject is lost to follow-up

For the purpose of medical management, all AEs and laboratory abnormalities that occur during the study will be evaluated by the Investigator. Each of these will be followed to satisfactory clinical resolution. Insofar as possible, all AEs will be followed-up to determine the final outcome of the event. The Investigator will follow-up all subjects with SAEs until the event has subsided (or disappeared), the condition has stabilized, the event is otherwise explained, or the subject is lost to follow-up.

Risk Benefit Analyses

The treatments given in this study will be the customary ones used for treatment of the iron deficiency anemia these patients with RLS-IAD. The study procedures involve minimal risks: rare complications from standard venous blood samples, psychological distress from the number of questionnaires and telephone calls and a risk of loss of confidentiality regarding participating in the study and the diagnosis of RLS. The blood samples will be obtained following standard procedures with standard treatment options provided for any adverse events occurring. These blood tests will be obtained as part of the routine care. Psychological distress will be minimized by advanced notice of the length, topics and timing of the questionnaires and interviews. The data when processed for review outside of the Auerbach clinic will be de-identified to protect patient confidentiality.

The study will benefit the patient by treating the iron deficiency and possibly treating the RLS. It will also benefit others with IAD-RLS by possibly indicating which is the preferred treatment- oral of IV iron.

Statistical Analyses

The percentage responding will be evaluated for each drug condition to determine overall effect size at 6 weeks after treatment. This will be calculated for the IRLS scale and the PGI as change from baseline and for the CGI with response determined as much or very much improved (scores of 1 or 2). All scores greater than 2 on the CGI are considered to indicate no significant response. The onset of treatment will be described as the percentage showing much or very much improvement at each of the evaluations and by the change in IRLS score from baseline at each evaluation. The duration of treatment over the 12 month follow up will be described as the percentage of responders and the IRLS change from baseline at each time point for both oral and IV iron. The oral iron treatment will be stopped for all subjects at the 6-week time point.

The outcomes for the oral versus IV treatments at 6 weeks will be compared using a standard unpaired unequal variance t-test for the change in IRLS scores from baseline. The number of responders compared to no-responders will be compared using the Fisher Exact test.

Sample Size

Uncontrolled experience observing IDA patients with RLS indicated that about 80% responded to IV iron (about 1000mg dose) and 50% responded to standard oral iron treatment over 6 to 12 weeks. These percentage outcomes require a sample size of 70 (35 with each treatment) to provide a power of >80% with alpha = 0.05 to test for differences between these treatments. This was considered a reasonable sample to ascertain the effect size of the two treatments and to provide enough positive outcomes to evaluate time course for improvement with treatment and persistence of the treatment effect.

Breaking the blind

The randomization is in cohort blocks of 10, 5 with each treatment. The blind for the form of initial treatment will be broken for every cohort of 10 treated patients after all members of a cohort have completed the study. The blind may also be broken for specific subjects if the treatment information is needed for medical care of the patient.

Concomitant Medication

Permitted Medications

Throughout the study, the subject may take any concomitant medications or treatments deemed necessary to provide adequate supportive care. When the subject is found eligible for the study, he/she is not allowed to take the medicine listed below as prohibited medications. Any concomitant medications administered while the subject is participating in the study must be recorded on the source document and transcribed into the concomitant medication form.

Prohibited Medications

The following medication is not allowed from baseline and until week 6 as it could potentially affect the primary endpoint:

- Any iron supplementation other than investigational drug
- Dopaminergic treatment
- Opioids
- Anti-depressives
- Pain killers
- Cannabis
- Anti-convulsants including alpha-2-delta drugs
- Centrally active anti-histamines

1. Allen, R.P., et al., *MRI measurement of brain iron in patients with restless legs syndrome.* Neurology, 2001. **56**(2): p. 263-5.
2. Rizzo, G., et al., *Low brain iron content in idiopathic restless legs syndrome patients detected by phase imaging.* Mov Disord, 2013.

3. Earley, C.J., et al., *MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome.* Sleep Med, 2006. **7**(5): p. 458-61.
4. Schmidauer, C., et al., *Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome.* Ann Neurol, 2005. **58**(4): p. 630-4.
5. Sun, E.R., et al., *Iron and the restless legs syndrome.* Sleep, 1998. **21**(4): p. 371-7.
6. Allen, R.P., et al., *Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: A multi-centred, placebo-controlled preliminary clinical trial.* Sleep Medicine, 2011. **12**(9): p. 906-913.
7. Wang, J., et al., *Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study.* Sleep Med, 2009. **10**(9): p. 973-5.
8. Allen, R.P., et al., *The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia.* Am J Hematol, 2013. **88**(4): p. 261-4.
9. Allen, R.P., et al., *Restless legs syndrome prevalence and impact: REST general population study.* Arch Intern Med, 2005. **165**(11): p. 1286-92.
10. Schrier, S.L. and M. Auerbach *Treatment of anemia due to iron deficiency*. UpToDate, 2013.
11. Allen, R.P., et al., *Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey.* Sleep Med, 2009. **10**(10): p. 1097-1100.
12. Hening, W.A., et al., *Validation of the Hopkins telephone diagnostic interview for restless legs syndrome.* Sleep Med, 2008. **9**(3): p. 283-289.
13. Hays, R.D., et al., *Psychometric properties of the Medical Outcomes Study Sleep measure.* Sleep Medicine, 2005. **6**(1): p. 41-4.
14. Cuellar, N.G. and S.J. Ratcliffe, *A comparison of glycemic control, sleep, fatigue, and depression in type 2 diabetes with and without restless legs syndrome.* J Clin Sleep Med, 2008. **4**(1): p. 50-6.
15. Stewart, A.L., R.D. Hays, and J.E. Ware, Jr., *The MOS short-form general health survey. Reliability and validity in a patient population.* Med Care, 1988. **26**(7): p. 724-35.
16. Bjelland, I., et al., *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res, 2002. **52**(2): p. 69-77.
17. *Feraheme package insert* 2009, AMAG Pharmaceuticals, Inc.: Lexington, MA.
18. Spinowitz, B.S., et al., *Ferumoxytol for treating iron deficiency anemia in CKD.* J Am Soc Nephrol, 2008. **19**(8): p. 1599-605.
19. Provenzano, R., et al., *Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients.* Clin J Am Soc Nephrol, 2009. **4**(2): p. 386-93.