**Appendix E. Table 6. Evidence Table for secondary RLS: iron trials**

| **Study Characteristics****and Design** | **Inclusion/Exclusion criteria** | **Participant Characteristics** | **Intervention (daily dose) /Comparator (daily dose)** | **Risk of bias and Applicability** |
| --- | --- | --- | --- | --- |
| **Study ID**Grote, 200930**Geographical Location**:Sweden**Funding source**: Industry**Study Design**:parallel design, fixed dose**Duration**: 12 months | **Inclusion criteria:** * age between 18 and 70 years
* 4 cardinal RLS diagnostic criteria\*
* score of ≥10 on the IRLS
* S-ferritin concentration <30 μg/L. A study amendment issued after inclusion of 30 patients increased the threshold for S-ferritin to 45 μg/L according to previously published recommendations
* normal folic acid/ B12 vitamin serum values.

**Exclusion criteria:** * concomitant use of any drug treatment for RLS
* clinical or laboratory findings suggestive of secondary RLS
* any previously known clinically significant allergic reaction
* use of drug treatment known to induce RLS
* pregnancy
* specific contraindication for iron sucrose
 | **N**=60**Age** (mean yr): 46.5**Gender** (Male %): 12**Race/Ethnicity** (%): NR**Comorbidities**: NR**Criteria used to define RLS:** *see inclusion criteria***Baseline Severity**: moderate to severe. Baseline mean IRLS score: 24.6**Previous RLS medication history**: NR**Iron Status** (serum ferritin (μg/L)): 20.55 | **Intervention:** Intravenous iron sucrose 200 mg x 5 occasions over 3 weeks (n=29)**Comparator:** Placebo (intravenous saline) (n=31)**A.** **Change in Disease Status and Impact**IRLS Scale Score**B. Quality of life**NR**Subjective Sleep Quality**Epworth Sleepiness Scale **Definition of clinically significant Improvement:** responders had ≥50% IRLS score reduction (A post-hoc analysis) | **Assessment of Internal Validity**Sequence generation: adequateAllocation concealment: adequateBlinding: patients and investigators Incomplete outcome data: no Selective outcome reporting: no |
| **Study ID**Wang, 200931**Geographical Location:** Europe (43 hospitals and sleep clinics in: Austria, Belgium, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the UK) **Funding source:** Industry**Study Design:**Parallel group**Duration:** 12 weeks | **Inclusion criteria:** * RLS diagnosed with IRLS criteria\*
* RLS Severity; IRLS ≥11 (AND)

measured ferritin level of 15-7 5ng/ml**Exclusion criteria:** * pregnancy
* hemochromatosis, or other significant liver disease, end-stage renal disease or significant sleep disturbance for reasons other than RLS
* iron saturation less than 15%
* iron sulphate allergy
* hemoglobin levels less than 11.1 g/dL for females and 14g/dL for male
* current or recent treatment with iron sulfate as defined by more than 325 mg each day for at least half of the days in the past 2 months or any other potential medications for treatment of RLS.
 | **N**=18**Age** (mean (SD), yr): 59.2**Gender (Male %):** 39%**Race/Ethnicity (%):** NR**Comorbidities**: NR**Criteria used to define RLS**IRLSS diagnostic criteria**Baseline Severity:**moderate to severe. Baseline mean IRLS score: 24.1**Previous RLS medication history**: NR**Iron Status**: NR | **Intervention:** Oral ferrous sulfate 650 mg (n=11)**Comparator:** Placebo (n=7)All patients were also asked to take vitamin C 100 mg twice daily.**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale Score**B. Quality of life**NR**Subjective Sleep Quality**NR**Definition of clinically significant Improvement:** NR**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: adequateAllocation concealment: adequateBlinding of participants and personnel, outcome assessors yesIncomplete outcome data: noSelective outcome reporting: no**Reviewer Comments**Performed at Veterans Affairs Medical Center, included active duty personnel, retirees, or family members  |

IRLS = International RLS Study Group Rating Scale; NR = not reported; PGI = Patient Global Impression

\* The 4 critical criteria are: 1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs); 2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; 3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking stretching, at least as long as the activity continues; 4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).