**Appendix E. Table 5. Evidence Table for primary RLS: Cabergoline trials**

| **Study Characteristics**  **and Design** | **Inclusion/Exclusion criteria** | **Participant Characteristics** | **Intervention /Comparator** | **Study Quality and Applicability** |
| --- | --- | --- | --- | --- |
| **Study ID**  Trenkwalder, 200727  **Geographical Location**  Europe (Multicenter)  **Funding source:**  Industry  **Study Design:**  RCT-parallel group  **Duration:**  30 weeks | **Inclusion criteria:**   * age 18 to 75 years * RLS diagnosed with IRLSSG criteria * RLS Severity; IRLS>10 and   “severity at night” score ≥4 in the 11 point RLS-6 rating scale  **Exclusion criteria:**   * secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy) * established or suspected hypersensitivity to ergot alkaloids or non-response or intolerability to previous cabergoline or L-dopa therapy * concomitant use of drugs with a probable influence on RLS | **N**=362  **Age** (mean, yr): 57.8  **Gender (Male %):**  %  **Race/Ethnicity (%):**  white 100  **Comorbidities**:  NR  **Criteria used to define RLS**  IRLSSG diagnostic criteria  **Primary or secondary RLS:**  Idiopathic  **Baseline Severity:**  Moderate-Severe. Baseline mean IRLS score: 25.7  **Previous RLS medication history**:  NR  **Iron Status**:  NR | **Intervention:** Cabergoline 2-3 mg, 3 hours before bedtime (n=178)  **Comparator:** Levodopa 200-300 mg, in 2 doses, the first one 3 hrs before bedtime and the second administered at bedtime (n=183)    **Outcomes reported:**  A. **Change in Disease Status and Impact**  IRLS Scale Score  CGI-I scale Score  **B. Quality of life**  RLS QoL  **Subjective Sleep Quality**  NR  **Definition of clinically significant Improvement:**  NR  **Adverse Effects Reported:** yes  Augmentation assessed using ASRS rating scale | **Assessment of Internal Validity**  Sequence generation: adequate  Allocation concealment: adequate  Blinding of participants and personnel, outcome assessors yes  Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment  **Selective outcome reporting:** no  **Reviewer Comments**  Patients had to pass a placebo run-in phase of 1 week prior to baseline. 19% of all subjects had augmentation/time shift during previous RLS treatment. |
| **Study ID**  Oertel, 200628  **Geographical Location:**  Europe (Austria, Germany, Norway, Sweden, Netherlands)  **Funding source:**  Industry  **Study Design:**  RCT-Parallel group  **Duration:**  5 weeks | **Inclusion criteria:**   * Age 18-80 yrs * Idiopathic RLS diagnosed with IRLS criteria * Moderate-severe RLS indicated by IRLS scale score>10 ( AND) a RLS severity at night score of 4 or greater on a 11-point RLS-6 rating scale (AND) PLMS arousal index PLMS-AI >5per hour total sleep time   **Exclusion criteria:**   * Secondary RLS (iron deficiency, renal disease) or drugs suspected to cause such secondary forms * Patients who showed evidence of mimics of RLS * Idiopathic Parkinson disease, insulin-dependent diabetes mellitus, clinically relevant polyneuropathy, liver disease, history of sleep apnea or malignancy, pleural effusions or fibrosis * Established or suspected hypersensitivity to ergot alkaloids * Pretreatment with Cabergoline * Women who were pregnant, or lactating or at risk for pregnancy during course of study | **N**=40  **Age** (mean (SD), yr): 56.4  **Gender (Male %):** 27  **Race/Ethnicity (%):**  NR  **Comorbidities**:  NR  **Criteria used to define RLS**  IRLSSG diagnostic criteria  **Primary or secondary RLS:**  Primary  **Baseline Severity:**  Severe-very severe. Baseline mean IRLS score: 31.5  **Previous RLS medication history**:  Patients with previous RLS treatment  I:95%  C:80%  **Iron Status**:  NR | **Intervention** Cabergoline (n=20)  2mg/day, once daily, at least 3 hrs before bedtime. Starting dose of 0.5mg/day up titrated to 2.0mg/day over a period of 2 wks.  **Comparator** Placebo (n=20)  **Outcomes reported:**  A. **Change in Disease Status and Impact**  IRLS Scale Score  **B. Quality of life**  QoL RLS  **Subjective Sleep Quality**  NR (Study only reports a subscale of SF-A)  **Definition of clinically significant Improvement:**  Responders defined as patients with at least 50% reduction of their baseline IRLS score or those who assessed their condition at week 6 as “much better” or “very much better” on patient global impressions scale  **Adverse Effects Reported:** yes | **Assessment of Internal Validity**  Sequence generation: adequate  Allocation concealment: adequate  Blinding of participants and personnel, outcome assessors yes  Incomplete outcome data: yes, had to have received at least one dose of study drug, had a baseline IRLS score and at least 1 post-baseline IRLS assessment  Selective outcome reporting: no  **Applicability**  Study participant had severe RLS, severe night time symptom scores and periodic limb movements of sleep  **Reviewer Comments**  63% of all subjects had drug-related augmentation during previous RLS treatment. |
| **Study ID**  Stiasny-Kolster, 200429  **Geographical Location:**  Germany, Multicenter  **Funding source:**  Industry and Govt.  **Study Design:**  RCT-Parallel group  Dose-ranging study with 3 different intervention arms  **Duration:**  5 weeks | **Inclusion criteria:**   * Age 18-75 yrs * Idiopathic RLS diagnosed with IRLS criteria * RLS Severity; IRLS>15 and a RLS severity at night≥4 on 11 point RLS-6 scale   **Exclusion criteria:**   * Patients with uremia, iron deficiency and rheumatoid arthritis * Patients with idiopathic Parkinson’s syndrome, insulin-dependent diabetes, polyneuropathy, liver disease, history of sleep apnea, malignancy, pleural effusions or fibrosis, and established or suspected hypersensitivity to ergot alkaloids * Women who were pregnant, at risk for pregnancy or lactating * Concomitant medications that influence sleep architecture or motor manifestations during sleep within the last week before baseline visit and during the trial. These include: neuroleptics, dopamine agonists, L-dopa, hypnotics, antidepressants, anxiolytics, anticonvulsants, psychostimulant medications and opioids. | **N**=86  **Age** (mean, yr): 56.1  **Gender (Male %):** 30%  **Race/Ethnicity (%):**  NR  **Comorbidities**:  NR  **Criteria used to define RLS**  IRLSSG diagnostic criteria  **Primary or secondary RLS:**  Primary  **Baseline Severity:**  Moderate-Severe. Baseline mean IRLS score: 26.6  **Previous RLS medication history**: Patients with previous RLS treatment 63.5%  **Iron Status**:  NR | **Intervention:** Cabergoline in 3 different doses: 0.5 mg/day (n=21); 1.0 mg/day (n=20); and 2.0 mg/day (n=22)  **Comparator:** Placebo (n=22)  **Outcomes reported:**  A. **Change in Disease Status and Impact**  IRLS Scale Score  **B. Quality of life**  NR  **Subjective Sleep Quality**  NR (Sleep diaries were used to document quality and duration of sleep; but they did not use a validated sleep scale)  **Definition of clinically significant Improvement:**  Remitters defined as those IRLS scale score=0  **Adverse Effects Reported:** yes | **Assessment of Internal Validity**  Sequence generation: adequate  Allocation concealment: adequate  Blinding of participants and personnel, outcome assessors yes  Incomplete outcome data:yes, “7 withdrawn from study as they fulfilled definition of non-responders”; To be included in the analysis patients had to have at least 1 assessment.  **Selective outcome reporting:** no |

IRLS = International RLS Study Group Rating Scale; NR = not reported