**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 ScoreCGI-I scale Score**B. Quality of life**RLS QoL**Subjective Sleep Quality**NR**Definition of clinically significant Improvement:** NR**Adverse Effects Reported:** yesAugmentation assessed using ASRS rating scale | **Assessment of Internal Validity**Sequence generation: adequateAllocation concealment: adequateBlinding of participants and personnel, outcome assessors yesIncomplete 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 treatmentI: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: adequateAllocation concealment: adequateBlinding of participants and personnel, outcome assessors yesIncomplete 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 assessmentSelective 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 groupDose-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: adequateAllocation concealment: adequateBlinding of participants and personnel, outcome assessors yesIncomplete 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