**Appendix E. Evidence Tables**

**Appendix E. Table 1. Evidence Table for primary RLS: dopamine agonist trials**

| **Study Characteristics****and Design** | **Inclusion/Exclusion criteria** | **Participant Characteristics** | **Intervention (daily dose) /Comparator (daily dose)** | **Risk of bias and Applicability** |
| --- | --- | --- | --- | --- |
| **Study ID**Bassetti, 20111**Geographical Location**: Switzerland**Funding source**: Industry**Study Design**:crossover**Duration**: two treatment periods of 4 weeks | **Inclusion criteria**: * Adults 25 to 85 years of age, meeting diagnostic criteria of the IRLS.
* RLS symptoms almost every day
* *de novo* patients

**Exclusion criteria**: none stated | **N**=67 (demographic information only for 39 patients in the per protocol population)**Age** (mean yr): 57**Gender (Male %)**: 41**Race/Ethnicity** (%): White 100%**Comorbidities**: NR**Criteria used to define RLS***See inclusion criteria***Baseline Severity**: moderate to severe. Baseline mean IRLS score: 21. 15 patients had severe RLS (score >20) with a mean baseline mean IRLS score of 26**Previous RLS medication history**: 0% (see inclusion criteria) | **Intervention:** Pramipexole 0.125 mg and could be increased up to 0.75 mg (3 capsules) if tolerated and needed or decreased due to side effects.Mean daily dose was 0.49 mg.**Comparator:** Levodopa/ beserazide 125-375 mg (initiated at 100/25 mg) and could be increased up to 3 capsules) if tolerated and needed or decreased due to side effects.Mean daily dose was 192/48 mg.**A.** **Change in Disease Status and Impact**IRLS Scale Score**B. Quality of life**SF-36**Subjective Sleep Quality**Epworth Sleepiness Scale**Definition of clinically significant Improvement:** NR**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: unclearAllocation concealment: adequateBlinding: patients and personnelIncomplete outcome data: yes, 28 patients excluded from the analyses (42%)Selective outcome reporting: yes (no CGI reported)**Reviewer Comments**Very large dropout rate**Notes**Sponsor participated in the design and conduct of the study and in the management of the data |
| **Study ID**Benes, 20112**Geographical Location**: Germany**Funding source**: Industry**Study Design**:parallel design, dose-titration**Duration**: 12 weeks | **Inclusion criteria**: * aged 18-80 years of age with moderate to severe idiopathic RLS meeting diagnostic criteria of the IRLS (IRLS score ≥15 and ≥11 on the RLS Diagnostic Index
* experienced ≥15 nights with symptoms of RLS in the previous 4 weeks or, if receiving treatment at screening, reported that they had symptoms of this frequency before treatment. In nights with RLS symptoms, patients had slept < 6 hours per night
* mild depressive symptoms indicated by C12 points on the Montgomery–Asberg Depression Rating Scale

**Exclusion criteria**: * secondary RLS (e.g., caused by renal insufficiency or iron insufficiency with baseline serum ferritin level <10 ng/ml)
* other movement or primary sleep disorders
* patients requiring treatment for RLS during the day/time clinically relevant DSM-IV psychiatric disorder like schizophrenia, bipolar disorder, or substance abuse
* pregnant, not using effective contraception or suffering from medical conditions that would affect assessment (e.g., independent pain syndromes)
 | **N**=266**Age** (mean yr): 58.5**Gender (Male %)**: 29**Race/Ethnicity** (%): NR**Comorbidities**: mild depressive symptoms**Criteria used to define RLS***See inclusion criteria***Baseline Severity**: moderate to severe. Baseline mean IRLS score: 28.6**Previous RLS medication history**: NR (not an exclusion) | **Intervention**: Ropinirole 0.25-4.0 mg/d (n=199). Patients who could not tolerate the 0.5mg dose were discontinued from the study.Mean daily dose was 1.9 mg.**Comparator:** Placebo (n=67)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI-I Scale Score**B. Quality of life**NR**Subjective Sleep Quality**MOS sleep scale**Definition of clinically significant Improvement:** Responders defined as 1) ≥6 point reductions on the IRLS score from baseline, and 2) those who rated very much improved or much improved on CGI-I or PGI scale scores**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: adequateAllocation concealment: adequateBlinding: patients and personnelIncomplete outcome data: yes, 35 patients excluded from the analyses (13%) – modified ITT (one study dose and one post-baseline assessment)Selective outcome reporting: no**Applicability:** patients with high RLS severity and comorbid depressive symptoms |
| **Study ID**Högl, 20113**Geographical Location**: Europe**Funding source**: Industry**Study Design**:parallel design, dose-titration**Duration**: 26 weeks | **Inclusion criteria**: * Adults 18 to 85 years of age, meeting diagnostic criteria of the IRLS (>15 points) and have experienced RLS symptoms 2-3 days/week throughout the previous 3 months.

**Exclusion criteria**: * serum ferritin ≤ 30 ng/mL
* known hypersensitivity to pramipexole
* augmentation during previous RLS treatment, unsuccessful previous treatment with non-ergotamine dopamine agonists (e.g. pramipexole, ropinirole)
* any non-RLS sleep disorder
* any major psychiatric disorder within last 2 years, change in any antidepressant regimen with last 4 weeks (or any anticipated change)
* any use of dopamine agonists, levodopa, or any medication or dietary supplement capable or altering RLS symptoms
* women with child bearing potential (pregnant, breastfeeding women, inadequate contraception)
 | **N**=331 (2 patients not included in demographic data)**Age** (mean yr): 56.9**Gender (Male %)**: 40.4**Race/Ethnicity** (%): NR**Comorbidities**: NR**Criteria used to define RLS***See inclusion criteria***Baseline Severity**: moderate to severe. Baseline mean IRLS score: 23.7**Previous RLS medication history**: NR (see exclusion criteria)**Iron Status**: patients with serum ferritin ≤30 ng/m excluded | **Intervention:** Pramipexole 0.125 mg and could be increased up to 0.75 mg based on clinically efficient response (PGI) (n=166)**Comparator:** Placebo (n=163)**A.** **Change in Disease Status and Impact**IRLS Scale ScoreCGI Scale Score**B. Quality of life**RLS-QoL**Subjective Sleep Quality**RLS-6**Definition of clinically significant Improvement:** 4.5 point difference between pramipexole and placebo at week 26**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: not defined Allocation concealment: not defined Blinding: patients and personnel Incomplete outcome data: yes, 2 patients did not receive any treatmentSelective outcome reporting: no |
| **Study ID**Montagna, 20114**Geographical Location:** International (52 hospitals, specialist offices, and primary care centers in Finland, France, Germany, Ireland, Italy, Korea, Spain , Sweden and the United Kingdom)**Funding source:** Industry**Study Design:**Parallel group**Duration:** 12 weeks | **Inclusion criteria:** * age 18 to 80 years
* RLS diagnosed with IRLSSG criteria
* RLS Severity; IRLS>15 (AND)
* IRLS item 10 scale score≥ 2 (i.e., at least moderate RLS-associated mood disturbance)
* RLS symptoms present ≥2 days per week during the prior two months

**Exclusion criteria:** * patients with baseline Beck Depression Inventory-II score >28, with current presence of major depression, psychosis, or any other severe mental disorder requiring medical therapy or history of suicidal ideation
* any clinical condition that could interfere with study participation or evaluation of results or that could increase patient’s health risk
* concomitant or prior treatment (within 2 wks) with any drug that could influence RLS symptoms or depressive symptoms (e.g., anxiolytics or hypnotics) was forbidden
* pregnant or breast feeding women
 | **N**=362**Age** (mean, yr): 55.5**Gender (Male %):** 30**Race/Ethnicity (%):** White 86%, Asian 13%**Comorbidities**: NR**Criteria used to define RLS**IRLSSG diagnostic criteria**Baseline Severity:**Severe RLSBaseline mean IRLS score: 25.9**Previous RLS medication history**: Previous treatmentI: 27.5%C:29.1%**Iron Status**: NR | **Intervention:** Pramipexole (n=203), daily, 1-3 hrs before bedtime. Dose started at 0.25 mg/day and titrated upwards during weeks 1 to 7 until patients were receiving maximum dose (4.0 mg/day) or optimal dose**Comparator:** Placebo (n=201)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale Score**B. Quality of life**RLS QoL**Subjective Sleep Quality**NR**Definition of clinically significant Improvement:** Responders for IRLS scale score defined as those with ≥50% improvement from baseline **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 and at least 1 post-baseline IRLS assessmentSelective outcome reporting: no |
| **Study ID**Hening, 20105**Geographical Location:** US**Funding source:** Industry**Study Design:**Parallel group, fixed-dose**Duration:** 6 months | **Inclusion criteria:*** age 18 to 75 years
* idiopathic RLS diagnosed with IRLS criteria
* de novo patients (no pervious dopaminergic medication) or positive response to dopaminergic treatment (excluding rotigotine)
* ≥15 points on IRLS scale, a score of ≥4 on CGI item 1 for disease severity

**Exclusion criteria**: * secondary RLS
* current history of sleep disorders
* treatment with dopamine agonists within 28 days or levodopa within 7 days prior to baseline visit
* concomitant treatment with hypnotics, antidepressants, anxiolytics, anticonvulsives, opioids, benzodiazepines, monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors, sedative antihistamines, psycho-stimulants, or amphetamines. Treatment with any of these drugs required a washout period of at least 7 days prior to baseline
* concomitant diseases such as polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs and moving toes, or radiculopathy; other central nervous system diseases such as Parkinson’s disease, dementia, progressive supranuclear paresis, multisystem atrophy, Huntington’s Chorea, amyotrophic lateral sclerosis, or Alzheimer’s disease
* previous psychotic episodes
* skin hypersensitivity to adhesives or other transdermals
* myocardial infarction over the previous 12 months
* clinically relevant cardiac, renal or hepatic dysfunction; arterial peripheral vascular disease
* a QTc interval ≥500 ms at screening or an average QTc ≥500 ms (3 measurements) at baseline; symptomatic orthostatic hypotension at screening or baseline
* any other condition which may jeopardize or compromise the subject’s ability to participate in the trial
* pregnant or lactating women, women without effective contraceptive methods
* subjects with work-related irregular sleep patterns
 | **N**=505**Age (mean yr)**: 52.4**Gender (Male %):** 40**Race/Ethnicity (%):** White 94%**Comorbidities**: NR**Criteria used to define RLS**IRLS criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: 23**Previous RLS medication history**: 36%**Iron Status**: NR | **Intervention:** Rotigotine transdermal patch,0.5 mg/24 hour (n=99)1.0 mg/24 hour (n=101)2.0 mg/24 hour (n=99)3.0 mg/24 hour (n=106)**Comparator:** Placebo (n=100)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI Scale Score**B. Quality of life**RLS QoL**Subjective Sleep Quality**MOS Sleep **Definition of clinically significant Improvement:** Responders for IRLS scale score defined as those with ≥50% improvement from baseline **Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: adequateAllocation concealment: adequateBlinding of participants and personnel: yesIncomplete outcome data: yes, post-baseline data required or at least one dose for safety analysesSelective outcome reporting: no |
| **Study ID**Oertel, 20106**Geographical Location:** Europe (Austria, Finland, Germany, Italy and Spain) **Funding source:** Industry**Study Design:**Parallel group**Duration:** 4 weeks | **Inclusion criteria:** * Male and female subjects aged 18-75 yrs
* RLS diagnosed with IRLSSG criteria
* De novo subjects; i.e., no previous dopaminergic RLS treatment or previous positive response to dopaminergic RLS treatment
* PLM index (PLMI) score of ≥ 15 PLM/h time in bed as documented using polysomnography, AND IRLSSG rating scale score≥15 AND CGI item 1, severity of symptom score ≥4
* ability to remove/apply patches correctly and consistently

**Exclusion criteria:** * previous Rotigotine treatment
* secondary RLS
* history of sleep disturbances other than owing to RLS
* treatment with dopamine agonists within 28 days or levodopa within 7 days prior to baseline visit
* concomitant diseases such as attention deficit hyperactivity disorder, polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs or moving toes, or radiculopathy; other central nervous system disorders such as Parkinson’s disease, dementia, progressive supanuclear palsy, multiple system atrophy, Huntington’s chorea, Alzheimer’s.
* previous psychotic episodes
* skin hypersensitivity to adhesives or other transdermals
* clinically relevant cardiac, renal, or hepatic dysfunction; venous or arterial peripheral vascular disease; or symptomatic orthostatic hypertension
* concomitant treatment with neuroleptics, hypnotics, antidepressants, anxiolytics, anticonvulsants, budipine, opiods, benzodiazepenes, monoamine oxidase inhibitors, catechol-O-methlytransferase inhibitors, sedative antihistamines, psychostimulants, amphetamines, or dopamine antagonist antiemetics except domperidone.
* pregnant or nursing women; women without effective contraceptive methods
* subjects with work-related irregular sleep patterns
 | **N**=362**Age** (mean yr): 59.4**Gender (Male %):** 26**Race/Ethnicity (%):** NR**Comorbidities**: NR**Criteria used to define RLS**IRLS criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: 26 **Previous RLS medication history**: NR**Iron Status**: NR | **Intervention:** Rotigotine transdermal patch, dose ranging from 1 mg/24 hour to optimal dose or a maximum dose of 3mg/ 24hr (n=46)**Comparator:** Placebo (n=20)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale Score% of responders on CGI-I scale Score**B. Quality of life**NR**Subjective Sleep Quality**MOS sleep scale**Definition of clinically significant Improvement:** Responders defined as: * ≥50% score improvement in IRLS scale at the end of maintenance phase vs. baseline

Remitters* IRLSSG rating scale≤10 or IRLS score =0 at the end of maintenance

**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 medication, a valid baseline assessment and at least 1 post-baseline assessmentSelective outcome reporting: no**Notes** “sponsor was involved in the design of the study, analysis and interpretation of the data, writing of the report, and in the decision to submit the paper for publication” |
| **Study ID**Ferini-Strambi, 20087Geographical Location: EuropeFunding source: IndustryStudy Design:parallel design, flexible doseDuration: 12 weeks | **Inclusion criteria**: * adults,18 to 80 years of age, meeting diagnostic criteria of the IRLS (>15 points) and have experienced RLS symptoms 2-3 days/week throughout the previous 3 months.

**Exclusion criteria**: * clinically significant liver or renal disease, insulin-dependent diabetes, clinically significant laboratory abnormalities
* present or past history of another sleep disorder
* major depression, psychiatric disorders, suicidal behavior/ ideation
* malignant melanoma
* women who were pregnant, lactating, or of child bearing potential and did not use or had inadequate contraception
* current use of medications that might affect RLS symptoms (e.g. levodopa, dopamine agonists, or antidepressants)
 | **N**=369**Age** (mean yr): 56.6**Gender** (Male %): 32**Race/Ethnicity** (%): white 99.5**Comorbidities**: NR**Criteria used to define RLS***See inclusion criteria***Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 24.4**Previous RLS medication history**: 26.6%**Iron Status**: NR | **Intervention**: Pramipexole 0.125 mg and could be increased up to 0.75 mg based on clinically efficient response (PGI) and tolerability (n=182)**Comparator:** Placebo (n=187)**A.** **Change in Disease Status and Impact**IRLS Scale ScoreCGI Scale ScorePGI Scale Score**B. Quality of life**RLS-QoL**Subjective Sleep Quality**Medical Outcomes Study (MOS) Sleep Scale**Definition of clinically significant Improvement:** none**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: adequateAllocation concealment: adequate (blister packs)Blinding: patients, investigators, and study personnel, Incomplete outcome data: Selective outcome reporting: no |
| **Study ID**Kushida, 20088**Geographical Location:** USAMulti center trial**Funding source:** Industry**Study Design:**Parallel group**Duration:** 12 weeks | **Inclusion criteria:** * age 18 to 79 years
* RLS diagnosed with IRLS criteria, IRLS >20 points
* baseline score ≥15 on the Insomnia severity index
* symptom onset no later than 5 pm
* ≥15 nights of RLS symptoms during the previous month

**Exclusion criteria:** * secondary RLS
* patients who had experienced augmentation or rebound with previous treatment
* patients with other primary sleep disorders, movement disorders or medical conditions that would affect the assessment of RLS
* experiencing daytime RLS symptoms that required treatment
* taking medications known to affect RLS or sleep
* experiencing withdrawal/ introduction/dose change of medications known to inhibit or induce P450CYP1A2
 | **N**=362**Age** (mean yr): 50.9**Gender** (Male %):40 **Race/Ethnicity (%):** NR**Comorbidities**: NR**Criteria used to define RLS**IRLS criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: 26**Previous RLS medication history**: NR**Iron Status**: NR | **Intervention**: Ropinirole 0.5-6.0 mg/d administered in divided doses (n=175)**Comparator:** Placebo (n=184)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale Score% of responders on CGI-I scale Score**B. Quality of life**NR**Subjective Sleep Quality****xx****Definition of clinically significant Improvement:** Responders defined as those who rated very much improved or much improved on CGI-I or PGI scale scores**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: NRAllocation concealment: NRBlinding of participants and personnel, outcome assessors NRIncomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessmentSelective outcome reporting**:** no**Reviewer Comments**No description of randomization procedures and no description of participant baseline characteristics except for age, gender and disease severity |
| **Study ID**Oertel, 20089**Geographical Location**: Europe**Funding source**: Industry**Study Design**:parallel design, fixed-dose**Duration**: 6 weeks | **Inclusion criteria:** * 18 and 75 (inclusive) years of age; met the diagnosis of idiopathic RLS based on the revised four essential diagnostic criteria according to the IRLS Study Group
* no previous treatment for RLS (de novo patients or intermittently untreated patients) or, if pretreated, had responded previously, according to medical history information, levodopa therapy and/or treatment with a dopamine agonist
* had a body mass index (BMI) between 18 and 35 kg/m2
* IRLS sum score of ≥15 (at least moderate RLS) at baseline.

**Exclusion criteria:** * secondary RLS associated with, for example, end-stage renal disease or iron-deficiency anemia
* history of sleep disturbances if not caused by RLS
* other concomitant neurological (e.g., symptoms or signs of polyneuropathy) or central nervous diseases or psychotic episodes
* concomitant therapy with neuroleptics, hypnotics, antidepressants, anxiolytic drugs, anticonvulsive therapy, psycho-stimulatory drugs, levodopa or opioids was prohibited and must have been washed out for a sufficient period of time (at least 7 days or at least five half-lives if longer) at baseline. Pretreatment with dopamine agonists had to be discontinued four weeks prior to enrollment. In addition, patients who had a medical history indicating intolerability to prior dopaminergic therapy (if pretreated) were excluded
* QTc-interval in resting ECG >450 ms in males and >470 ms in females, history of symptomatic orthostatic hypotension within 28 days prior to screening, or a systolic blood pressure <105 mmHg at trial entry.
 | **N**=341 (demographic information on 333)**Age** (mean yr): 58.4**Gender** (Male %):33**Race/Ethnicity (%):** NR**Comorbidities**: NR**Criteria used to define RLS**IRLS criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: 27.9**Previous RLS medication history**: 80.8%. Previous augmentation 25.5%**Iron Status**: NR | **Intervention:** Rotigotine transdermal patch,0.5 mg/24 hour (n=52)1.0 mg/24 hour (n=64)2.0 mg/24 hour (n=49)3.0 mg/24 hour (n=65)4.0 mg/24 hour (n=56)**Comparator:** Placebo (n=55)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI Scale Score**B. Quality of life**RLS QoL**Subjective Sleep Quality**MOS Sleep **Definition of clinically significant Improvement:** Responders for IRLS scale score defined as those with ≥50% improvement from baseline **Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: adequateAllocation concealment: adequate (blister packs)Blinding: patients, investigatorsIncomplete outcome data: yes, efficacy and safety analysis was performed for allpatients who were treated with at least one dose of trialmedication |
| **Study ID**Trenkwalder, 200810**Geographical Location:** Europe (49 centers in Austria, Finland, Germany, Italy, Netherlands, Spain, Sweden, UK) **Funding source:** Industry**Study Design:**Parallel group, fixed-dose**Duration:** 6 months | **Inclusion criteria:** * age 18 to 75 years
* idiopathic RLS diagnosed with IRLS criteria
* either no pervious dopaminergic medication for RLS or positive response to dopaminergic treatment
* ≥15 points on IRLS scale, a score of ≥4 on CGI item 1 for disease severity
* ability to remove apply patches correctly and consistently

**Exclusion criteria:** * secondary RLS
* current history of sleep disturbances (sleep apnea syndrome, narcolepsy,
* concomitant treatment with several types of drug (neuroleptics, hypnotics, antidepressants, anxiolytics, anticonvulsives, opioids, benzodiazepines, monoamine oxidase inhibitors, catechol-O methyltransferase inhibitors, sedative anti histamines, psychostimulants,

or amphetamines)* concomitant diseases

such as polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs and moving toes, orradiculopathy; other CNS diseases (eg, Parkinson’s disease,dementia, progressive supranuclear palsy, multisystematrophy, Huntington’s disease, amyotrophic lateralsclerosis, or Alzheimer’s disease);* previous psychotic episodes
* skin hypersensitivity to adhesives or other transdermal preparations;
* myocardial infarction over the past 12 months
* clinically relevant cardiac, renal or hepatic dysfunction
* arterial peripheral vascualar disease
* Qtc interval of 500 ms or longer at screening
* symptomatic orthostatic hypotension at screening or baseline
* intake of investigational drug 28 days before baseline visit
* pregnant or lactating women
* women without effective contraceptive methods
* patients with work-related irregular sleep patterns
 | **N**=458**Age** (mean, yr): 57.7**Gender (Male %):** 27**Race/Ethnicity (%):** White 99**Comorbidities**: NR**Criteria used to define RLS**IRLSSG diagnostic criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: 28.1 **Previous RLS medication history**: NR**Iron Status**: NR | **Intervention:** Rotigotine 1mg/24hr (n=115)Rotigotine 2mg/24 hr (n=112)Rotigotine 3mg/24 hr (n=114)**Comparator:** Placebo (n=117)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI-I scale Score**B. Quality of life**RLS QoLGeneric health related quality of life SF-36)**Subjective Sleep Quality**MOS sleep scale**Definition of clinically significant Improvement:** Remission (IRLS sum score=0 or <10 )Responders defined as having minimum 50% improvement from baseline in IRLS score or a CGI item 2 rating of “much improved”**Adverse Effects Reported:** yesSeverity of Augmentation assessed with ASRS scale score | **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 assessmentSelective outcome reporting: no**Reviewer Comments**Not ITT; patients analyzed different from patients randomized. Study sponsor involved in conception and design of the study and in data analysis and interpretation but had no role in data collection  |
| **Study ID**Oertel, 200711**Geographical Location**: Europe**Funding source**: Industry**Study Design**:parallel design, dose-response**Duration**: 6 weeks | **Inclusion criteria**: * male and female patients, 18 to 80 years of age, with a diagnosis of primary RLS based on IRLS criteria (score >15 points)
* RLS symptoms present for at least 2 to 3 days per week in the 3 months before study entry.

**Exclusion criteria**: * pregnant, breastfeeding women or using inadequate contraception
* diabetic or had significant renal, hepatic, gastrointestinal, pulmonary, or endocrine disorders, other neurologic disease
* sleep disorders unrelated to RLS, psychotic disorders
* mental disorders, patients with a history of substance abuse.
 | **N**=345**Age** (mean yr): 55.5**Gender** (Male %): 34**Race/Ethnicity** (%): white 99**Comorbidities**: NR**Criteria used to define RLS***See inclusion criteria***Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 24.8**Previous RLS medication history**: 31%. All pharmacologic treatmentfor RLS was discontinued within 14 days before the study’s start**Iron Status**: NR | **Intervention:** Pramipexole 0.125 mg and could be increased up to 0.75 mg according to the Patient Global Impression scale (PGI) rating and overall tolerability of the drug (n=230)**Comparator:** Placebo (n=115)**A.** **Change in Disease Status and Impact**IRLS Scale ScoreCGI Scale Score**B. Quality of life**NR**Subjective Sleep Quality**none**Definition of clinically significant Improvement:** IRLS responders if they had an at least 50% reduction in their baseline IRLS score at week 6**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: not defined Allocation concealment: not defined Blinding: patients and personnelIncomplete outcome data: yes, had to have received one dose of study drugSelective outcome reporting: no |
| **Study ID**Adler, 200412**Geographical Location**: US**Funding source**: Industry**Study Design**:crossover**Duration**: 4 weeks of placebo then ropinirole or ropinirole then placebo with a 1-week wash-out betweentreatments | **Inclusion criteria**: * IRLS criteria for RLS and needed a IRLS score ≥10. Patients were not allowed to be on RLS medication for at least 2 weeks prior to the baseline visit.

**Exclusion criteria**: * previous use of ropinirole, secondary RLS
* significant medical disease that would not allow use of ropinirole
* an inability to complete diary forms
* pregnancy or lactation.
 | **N**=22**Age** (mean yr): 60 **Gender** (Male %): 27**Race/Ethnicity** (%): NR**Comorbidities**: NR**Criteria used to define RLS**baseline total score ≥10 points on IRLS**Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 25.9**Previous RLS medication history**: NR, none with ropinirole | **Intervention:** Ropinirole 0.5 to 6.0 mg (mean dose was 4.6 mg), administered in divided doses (n=22). **Comparator:** Placebo (n=22)**A.** **Change in Disease Status and Impact**IRLS Scale ScoreGlobal change score (-3 markedly worse to +3 markedly improved)**B. Quality of life**none**Subjective Sleep Quality**Epworth Sleepiness Scale**Definition of clinically significant Improvement:** none**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: not definedAllocation concealment: adequate, packaging identical in appearanceBlinding: patients, investigatorsIncomplete outcome data: noSelective outcome reporting: no |
| **Study ID**Bogan, 200613**Geographical Location**: US**Funding source**: Industry**Study Design**:parallel design, flexible dose**Duration**: 12 weeks | **Inclusion criteria**: * adults, aged 18 to 79 years, with a diagnosis of primary RLS, using the IRLS diagnostic criteria (baseline total score ≥15 points
* ≥15 nights of RLS symptoms during the previous month, and documented RLS symptoms for at least 4 of the 7 nights during the screening/ washout phase (between the screening visit and baseline visit)).

**Exclusion criteria**: * signs of secondary RLS, including renal failure, pregnancy, and iron deficiency anemia. Iron deficiency was determined by each investigator based on clinical judgment of serum iron, ferritin, iron binding capacity, and percent saturation data obtained in each patient at screening.
* patients who had experienced augmentation or rebound with previous treatment or had daytime symptoms as a part of their usual RLS symptom pattern were also excluded.
 | **N**=381**Age** (mean yr): 52.3 **Gender** (Male %): 39**Race/Ethnicity** (%): NR**Comorbidities**: NR**Criteria used to define RLS***See inclusion criteria***Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 22**Previous RLS medication history**: NR but patients who had experienced augmentation or rebound with previous treatment were excluded**Iron Status**: subjects with iron deficiency anemia excluded | **Intervention:** Ropinirole 0.25-4.0 mg (n=187)**Comparator:** Placebo (n=194)**A.** **Change in Disease Status and Impact**IRLS Scale ScoreCGI Scale Score**B. Quality of life**Johns Hopkins RLS Quality ofLife questionnaire**Subjective Sleep Quality**Medical Outcomes Study (MOS) Sleep Scale**Definition of clinically significant Improvement:** NR**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: not definedAllocation concealment: adequate, packaging identical in appearanceBlinding: patients, investigators, site monitors Incomplete outcome data: 1 patient from the placebogroup did not receive any study medication Selective outcome reporting: no |
| **Study ID**Montplasir, 200614**Geographical Location:** 18 centers in Australia, Austria, Canada, Germany and South Africa**Funding source:** Industry**Study Design:**Parallel group**Duration:** 12 wks(Trial consisted of 24-week single blind phase during which all patients received ropinirole followed by 12 wk double blind, placebo controlled phase for treatment responders defined as those with reduction in total IRLS score of at least 6 points from baseline) | **Inclusion criteria:** * age 18 to 80 years
* male or female patients
* RLS diagnosed with IRLS criteria (IRLS ≥15 points)
* ≥15 nights of RLS symptoms during the previous month; for patients who had been receiving treatment for RLS investigators used their best clinical judgment to assess whether or not the patient would have experienced a minimum of 15 nights of symptoms if the patient had not been treated

**Exclusion criteria:** * patients with other primary sleep disorders that might affect the symptoms of RLS
* patients with movement disorders
* patients with a medical condition that would affect assessment of RLS or the tolerability of ropinirole
* experiencing daytime RLS symptoms that required treatment
* experiencing augmentation or end of dose rebound from previous therapy
* secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy
* history of alcohol or drug abuse
* previous intolerance to dopamine agonists
 | **N**=362**Age** (mean (SD), yr): 53.5**Gender (Male %):** 45**Race/Ethnicity (%):** NR**Comorbidities**: NR**Criteria used to define RLS**IRLSSG diagnostic criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: initially 26 (single-blind phase) **Previous RLS medication history**: NR**Iron Status**: NR | **Intervention** Ropinirole (n=45) daily, 1-3 hrs before bedtime.Doses started at 0.25mg/day and titrated upwards to a maximum dose of 4 mg/day.**Comparator:** Placebo (n=47)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI-I scale Score**B. Quality of life**RLS QoLGeneric health related quality of life SF-36)**Subjective Sleep Quality**MOS sleep scale**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: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessmentSelective outcome reporting: no |
| **Study ID**Winkelman, 200615**Geographical Location:**United States Multicenter Trial(43 Sites)**Funding source:** Industry**Study Design:**Parallel group( 4 arms; comparison of 3 fixed doses of pramipexole with placebo)**Duration:**12 weeks | **Inclusion criteria:** * adults (age 18 to 80 years)
* RLS diagnosed with IRLSSG criteria
* moderate to severe disease; IRLS score>15 and symptoms at least 2 to 3 days per week for at least the previous 3 months

**Exclusion criteria:** * recent RLS treatment (concurrently or during the prior 2 wks)
* history of failed RLS treatment
* recent use of dietary supplement or medication with potential to affect RLS symptoms
* any medical condition that could affect assessment or contraindicate pramipexole
* any sleep disorder other than RLS
 | **N**=345**Age** (mean, yr): 51.4 **Gender (Male %):** 38%**Race/Ethnicity (%):**%White=97.3**Comorbidities**: NR**Criteria used to define RLS**IRLSSG criteria**Baseline Severity:** Moderate-Severe disease. Baseline mean IRLS score: 23.5**Previous RLS medication history**: NR**Iron Status**: NR | **Intervention:** Pramipexole (n=254) at fixed doses of 0.25 (n=89), 0.5 (n=80) and 0.75 (n=90) mg/day, taken each evening 2 to 3hrs before anticipated bedtime**Comparator:** Placebo (n=86)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI-I Scale Score**B. Quality of life**RLS-QoL**Subjective Sleep Quality**Epworth Sleepiness Scale (ESS**)****Length of follow-up** **Definition of clinically significant Improvement:** Responder= patient with CGI-I score of very much improved or improved (or)at least 50% reduction in IRLS score from baseline**Adverse Effects Reported:** yes | **Assessment of Internal Validity**Sequence generation: adequate, computer generated randomization scheduleAllocation concealment: unclearBlinding of participants and personnel, outcome assessors YesIncomplete outcome data: yes, had to have received one dose of study drugSelective outcome reporting: no |
| **Study ID**Trenkwalder, 200416**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:** * age 18 to 79 years
* RLS diagnosed with IRLS criteria
* RLS Severity; IRLS>20
* baseline score≥ 15 on the Insomnia severity index

(AND)* ≥15 nights of RLS symptoms during the previous month, or if receiving treatment reported they had had symptoms of this frequency before treatment

**Exclusion criteria:** * patients with other primary sleep disorders or other clinically relevant conditions affecting assessments
* experiencing daytime RLS symptoms that required treatment
* experiencing augmentation or end of dose rebound
* secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy
* history of alcohol or drug abuse
* previous intolerance to dopamine agonists
 | **N**=362**Age** (mean (SD), yr): 55.1**Gender (Male %):** 37%**Race/Ethnicity (%):** NR**Comorbidities**: NR**Criteria used to define RLS**IRLSSG diagnostic criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: 24.8**Previous RLS medication history**: NR**Iron Status**: NR (secondary RLS de to iron deficiency an exclusion) | **Intervention** Ropinirole (n=147) daily, 1-3 hrs before bedtime.Dose starting at 0.25mg/day and titrated upwards during weeks 1 to 7 until patients were receiving maximum dose (4.0 mg/day) or optimal dose**Comparator:** Placebo (n=139)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI-I scale Score**B. Quality of life**RLS QoLGeneric health related quality of life SF-36)**Subjective Sleep Quality**MOS sleep scale**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: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessmentSelective outcome reporting: no**Applicability**Primary RLS patients with severe disease experiencing night time symptoms and insomnia |
| **Study ID**Walters, 200417**Geographical Location:** International, Multicenter (Australia, Europe, North America)**Funding source:** Industry**Study Design:**Parallel group**Duration:** 12 weeks | **Inclusion criteria:** * age 18 to 79 years
* RLS diagnosed with IRLSSG criteria
* RLS Severity; IRLS>20
* ≥15 nights of RLS symptoms during the previous month; if patient was undergoing treatment for RLS, then clinician judged whether or not patient would have experienced at least 15 nights of symptoms if they had not been treated

**Exclusion criteria:** * experiencing daytime RLS symptoms that required treatment
* experiencing augmentation or end of dose rebound with previous medication
* secondary RLS (end stage renal disease, iron deficiency anaemia or pregnancy
* other sleep disorders (e.g. narcolepsy, sleep terror disorder, sleep walking disorder, breathing related sleep disorder)
* medical conditions that would affect assessment of RLS (e.g., rheumatoid arthritis, fibromyalgia syndrome)
* known intolerance to ropinirole
* abusing other substances
 | **N**=267**Age** (mean (SD), yr): 55.5**Gender (Male %):** 40**Race/Ethnicity (%):** NR**Comorbidities**: NR**Criteria used to define RLS**IRLSSG diagnostic criteria**Baseline Severity:**Moderate-Severe. Baseline mean IRLS score: 24.2**Previous RLS medication history**: I:48.5%C: 43.4%**Iron Status**: NR | **Intervention** Ropinirole (n=131) daily, 1-3 hrs before bedtimeFlexible dosing starting at 0.25mg/day up to a maximum of 4mg/day.**Comparator:** Placebo (n=136)**Outcomes reported:**A. **Change in Disease Status and Impact**IRLS Scale ScoreCGI-I scale Score**B. Quality of life**RLS QoLQoL by SF-36, a generic quality of life instrument**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: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessmentSelective outcome reporting: no |

CGI = Clinical Global Impression; IRLS = International RLS Study Group Rating Scale; NR = not reported; PGI = Patient Global Impression; PLMS = periodic leg movements during sleep; SF-36 = Short-Form 36-item Questionnaire