**Table 93 TEAEs Reported for ≥ 2 % Either Treatment Group *(Safety Population: Controlled Adjunctive* Therapy [Study 169])**

| System Organ Class<br>Preferred Term | Treatment Groups for Controlled Adjunctive Therapy (Study 169) | | | |
|---|---|---|---|---|
| | Placebo n=191 | | Ropinirole CR n=202 | |
| | # Events | n (%) | # Events | n (%) |
| Any TEAE[1] | --- | 104 (54) | --- | 129 (64) |
| Nervous System Disorders, Any event | --- | 42 (22) | --- | 64 (32) |
| Dyskinesia | 7 | 5 (3) | 41 | 27 (13) |
| Dizziness | 7 | 6 (3) | 33 | 16 (8) |
| Somnolence | 7 | 7 (4) | 19 | 14 (7) |
| Headache | 8 | 7 (4) | 9 | 7 (3) |
| Tremor | 8 | 6 (3) | 4 | 3 (1) |
| Parkinson's disease | 7 | 5 (3) | 1 | 1 (<1) |
| Parkinsonism | 5 | 4 (2) | 1 | 1 (<1) |
| Psychiatric Disorders, Any event | --- | 28 (15) | --- | 39 (19) |
| Hallucination | 4 | 3 (2) [2] | 11 | 11 (5) |
| Insomnia | 7 | 7 (4) | 8 | 7 (3) |
| Depression | 5 | 5 (2) | 6 | 5 (2) |
| Abnormal dreams | 4 | 4 (2) | 5 | 5 (2) |
| Anxiety | 2 | 2 (1) | 5 | 5 (2) |
| Hallucination, visual | 2 | 2(1) | 9 | 4(2) |
| Sleep disorder | 4 | 4 (2) | 3 | 3 (1) |
| Confusional state | 4 | 4 (2) | 0 | 0 |
| Gastrointestinal Disorders, Any event | --- | 18 (9) | --- | 45 (22) |
| Nausea | 8 | 7 (4) | 34 | 23 (11) |
| Diarrhea | 5 | 4 (2) | 7 | 7 (3) |
| Constipation | 3 | 3 (2) | 8 | 8 (4) |
| Vomiting | 3 | 3 (2) | 6 | 5 (2) |
| Abdominal pain | 1 | 1 (<1) | 5 | 5 (2) |
| Dry mouth | 1 | 1 (<1) | 4 | 4 (2) |
| Musculoskeletal and Connective Tissue Disorders | --- | 26 (14) | --- | 21 (10) |
| Back pain | 5 | 4 (2) | 7 | 6 (3) |
| Pain in extremity | 4 | 4 (2) | 4 | 4 (2) |
| Arthralgia | 3 | 3 (2) | 5 | 3 (1) |
| Joint swelling | 4 | 3 (2) | 2 | 2 (<1) |
| Myalgia | 3 | 3 (2) | 2 | 2 (<1) |
| Osteoarthritis | 3 | 3 (2) | 0 | 0 |
| General Disorders and Administration Site Conditions, Any event | --- | 11 (6) | --- | 25 (12) |
| Edema peripheral | 2 | 2 (1) | 9 | 8 (4) |
| Asthenia | 4 | 3 (2) | 3 | 3 (1) |
| Fatigue | 4 | 3 (2) | 3 | 2 (<1) |
| Infections and Infestations, Any event | --- | 12 (6) | --- | 22 (11) |
| Nasopharyngitis | 4 | 4 (2) | 8 | 5 (2) |
| Influenza | 2 | 2 (1) | 2 | 2 (<1) |
| Urinary tract infection | 3 | 3 (2) | 3 | 3 (1) |
| Vascular Disorders, Any event | --- | 9 (5) | --- | 21 (10) |
| Orthostatic hypotension | 2 | 2 (1) | 13 | 10 (5) |
| Hypertension | 4 | 4 (2) | 6 | 6 (3) |
| Hypotension | 0 | 0 | 7 | 5 (2) |
| Injury, Poisoning and Procedural Complications, Any event | --- | 9 (5) | --- | 18 (9) |
| Fall | 2 | 2 (1) | 5 | 5 (2) |
| Contusion | 3 | 3 (2) | 1 | 1 (<1) |
| Respiratory, Thoracic and Mediastinal Disorders, Any event | --- | 10 (5) | --- | 6 (3) |
| Dyspnea | 6 | 5 (3) | 3 | 2 (<1) |
| Cough | 3 | 3 (2) | 1 | 1 (<1) |
| Ear and Labyrinth Disorders, Any event | --- | 7 (4) | --- | 8 (4) |
| Vertigo | 9 | 4 (2) | 11 | 8 (4) |

Data Sources: Table 5.79 (# events); Table 5.22 (n [%]); 169 Listing 6.1

Abbreviations: CR = controlled-release; N = total number of subjects; n = number of subjects; TEAE = treatment-emergent adverse event

Note: TEAE data were analyzed for incidence (ie, percentage of total number of subjects reporting a given event [n [%]] and total number of events reported (# events] for a given TEAE.

1. 'Any TEAE' refers to both non-gender- and gender-specific events with onset during any study period (excluding down-titration) regardless of potential relationship to study drug or intensity.

**Table 94 TEAEs with Onset During Any Study Period (Including Down-Titration) and Reported for ≥ 2 % Any Treatment Group (Pooled Safety Population: All Parkinson's Disease Studies)**

| System Organ Class | Treatment Groups for *All PD Studies* (Studies 164,165, 166, 167, 169, 228, 168 and 196)[1] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo N=191 | | Pooled Ropinirole CR N=613[1] | | Pooled Ropinirole IR N=209 | | Sinemet N=104 | |
| Preferred Term | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Any TEAE[2] | 285 | 106 (55) | 3246 | 449 (73) | 561 | 124 (59) | 382 | 86 (83) |
| Nervous System Disorders | | | | | | | | |
| Any event | 65 | 42 (22) | 706 | 258 (42) | 133 | 70 (33) | 73 | 47 (45) |
| Dizziness | 7 | 5 (3) | 158 | 92 (15) | 25 | 16 (9) | 15 | 15 (14) |
| Somnolence | 7 | 7 (4) | 142 | 82 (13) | 36 | 25 (12) | 6 | 6 (6) |
| Headache | 8 | 7 (4) | 131 | 73 (12) | 27 | 20 (10) | 12 | 9 (9) |
| Tremor | 8 | 6 (3) | 36 | 34 (6) | 8 | 8 (4) | 10 | 9 (9) |
| Dyskinesia | 7 | 5 (3) | 45 | 30 (5) | 0 | 0 | 2 | 2 (2) |
| Balance disorder | 1 | 1 (<1) | 16 | 14 (2) | 4 | 4 (2) | 1 | 1 (<1) |
| Parkinson's disease | 7 | 5 (3) | 13 | 11 (2) | 3 | 3 (1) | 0 | 0 |
| Paresthesia | 1 | 1 (<1) | 12 | 11 (2) | 3 | 3 (1) | 3 | 3 (3) |
| Hypoesthesia | 0 | 0 | 11 | 11 (2) | 2 | 2 (<1) | 3 | 2 (2) |
| Syncope | 0 | 0 | 6 | 6 (<1) | 6 | 5 (2) | 0 | 0 |
| Disturbance in attention | 0 | 0 | 8 | 4 (<1) | 1 | 1 (<1) | 2 | 2 (2) |
| Dizziness postural | 0 | 0 | 5 | 4 (<1) | 0 | 0 | 2 | 2 (2) |
| Parkinsonism | 6 | 4 (2) | 2 | 2 (<1) | 0 | 0 | 0 | 0 |
| Poor quality sleep | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Gastrointestinal Disorders | | | | | | | | |
| Any event | 35 | 19 (10) | 625 | 223 (36) | 169 | 67 (32) | 54 | 37 (36) |
| Nausea | 8 | 7 (4) | 250 | 139 (22) | 103 | 47 (22) | 19 | 16 (15) |
| Constipation | 3 | 3 (2) | 65 | 52 (8) | 9 | 7 (3) | 7 | 7 (7) |
| Diarrhea | 5 | 4 (2) | 53 | 42 (7) | 7 | 6 (3) | 4 | 4 (4) |
| Vomiting | 4 | 3 (2) | 43 | 35 (6) | 7 | 7 (3) | 2 | 2 (2) |
| Dyspepsia | 2 | 1 (<1) | 32 | 25 (4) | 14 | 12 (6) | 4 | 4 (4) |
| Dry mouth | 2 | 2 (1) | 22 | 21 (3) | 1 | 1 (<1) | 3 | 3 (3) |
| Abdominal pain | 1 | 1 (<1) | 25 | 22 (4) | 1 | 1 (<1) | 2 | 2 (2) |
| Flatulence | 0 | 0 | 26 | 16 (3) | 4 | 4 (2) | 0 | 0 |
| Abdominal pain upper | 1 | 1 (<1) | 16 | 11 (2) | 3 | 2 (<1) | 4 | 3 (3) |
| Musculoskeletal and Connective Tissue Disorders | | | | | | | | |
| Any event | 33 | 26 (14) | 322 | 152 (25) | 35 | 26 (12) | 55 | 32 (31) |
| Back pain | 5 | 4 (2) | 65 | 45 (7) | 5 | 5 (2) | 12 | 10 (10) |
| Arthralgia | 3 | 3 (2) | 46 | 36 (6) | 4 | 3 (1) | 10 | 9 (9) |
| Pain in extremity | 4 | 4 (2) | 49 | 37 (6) | 4 | 4 (2) | 5 | 5 (5) |
| Muscle spasms | 1 | 1 (<1) | 33 | 24 (4) | 3 | 3 (1) | 10 | 9 (9) |
| Shoulder pain | 2 | 2 (1) | 18 | 17 (3) | 1 | 1 (<1) | 1 | 1 (<1) |
| Myalgia | 3 | 3 (2) | 13 | 13 (2) | 1 | 1 (<1) | 1 | 1 (<1) |
| Joint swelling | 4 | 3 (2) | 9 | 9 (1) | 3 | 3 (1) | 3 | 1 (<1) |
| Musculoskeletal stiffness | 0 | 0 | 9 | 9 (1) | 2 | 2 (<1) | 2 | 2 (2) |
| Neck pain | 0 | 0 | 5 | 5 (<1) | 3 | 3 (1) | 3 | 3 (3) |
| Osteoarthritis | 3 | 3 (2) | 5 | 5 (<1) | 1 | 1 (<1) | 1 | 1 (<1) |
| Psychiatric Disorders | | | | | | | | |
| Any event | 36 | 29 (15) | 314 | 146 (24) | 38 | 26 (12) | 33 | 24 (23) |
| Insomnia | 7 | 7 (4) | 60 | 49 (8) | 12 | 8 (4) | 11 | 10 (10) |
| Depression | 5 | 5 (3) | 35 | 30 (5) | 8 | 6 (3) | 6 | 6 (6) |
| Hallucination | 4 | 3 (2)[3] | 39 | 36 (6) | 1 | 1 (<1) | 1 | 1 (<1) |
| Anxiety | 2 | 2 (1) | 28 | 24 (4) | 5 | 4 (2) | 4 | 4 (4) |
| Abnormal dreams | 4 | 4 (2) | 19 | 15 (2) | 2 | 2 (<1) | 2 | 2 (2) |
| Confusional state | 5 | 5 (3) | 14 | 12 (2) | 1 | 1 (<1) | 3 | 3 (3) |
| Sleep disorder | 4 | 4 (2) | 10 | 10 (2) | 2 | 2 (<1) | 0 | 0 |
| Nervousness | 0 | 0 | 3 | 3 (<1) | 2 | 2 (<1) | 2 | 2 (2) |
| General Disorders and Administration Site Conditions | | | | | | | | |
| Any event | 17 | 11 (6) | 304 | 139 (23) | 40 | 28 (13) | 26 | 21 (20) |
| Fatigue | 4 | 3 (2) | 58 | 42 (7) | 19 | 15 (7) | 10 | 9 (9) |
| Edema peripheral | 2 | 2 (1) | 78 | 49 (8) | 4 | 3 (1) | 1 | 1 (<1) |
| Asthenia | 4 | 3 (2) | 35 | 20 (3) | 3 | 2 (<1) | 2 | 2 (2) |
| Chest pain | 0 | 0 | 25 | 17 (3) | 0 | 0 | 2 | 2 (2) |
| Pain | 2 | 2 (1) | 11 | 10 (2) | 4 | 2 (<1) | 0 | 0 |
| Feeling abnormal | 0 | 0 | 4 | 4 (<1) | 1 | 1 (<1) | 2 | 2 (2) |
| Feeling cold | 0 | 0 | 3 | 3 (<1) | 1 | 1 (<1) | 2 | 2 (2) |
| Infections and Infestations | | | | | | | | |
| Any event | 16 | 12 (6) | 208 | 125 (21) | 26 | 20 (10) | 36 | 24 (23) |
| Nasopharyngitis | 4 | 4 (2) | 40 | 33 (5) | 7 | 6 (3) | 6 | 4 (4) |
| URT infection | 0 | 0 | 32 | 24 (4) | 1 | 1 (<1) | 8 | 7 (7) |
| Urinary tract infection | 4 | 4 (2) | 18 | 15 (3) | 3 | 3 (1) | 2 | 1 (<1) |
| Influenza | 2 | 2 (1) | 14 | 13 (2) | 3 | 3 (1) | 0 | 0 |
| Bronchitis | 1 | 1 (<1) | 14 | 14 (2) | 0 | 0 | 1 | 1 (<1) |
| Sinusitis | 0 | 0 | 11 | 11 (2) | 0 | 0 | 3 | 3 (3) |

**Table 94 (Continued) TEAEs with Onset During Any Study Period (Including Down-Titration) and Reported for ≥ 2 % Any Treatment Group (Pooled Safety Population: All Parkinson's Disease Studies)**

| System Organ Class / Preferred Term | Treatment Groups for All PD Studies (Studies 164,165, 166, 167, 169, 228, 168 and 196)[1] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo N=191 | | Pooled Ropinirole CR N=613[1] | | Pooled Ropinirole IR N=209 | | Sinemet N=104 | |
| | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Respiratory, Thoracic and Mediastinal Disorders | | | | | | | | |
| Any event | 13 | 10 (5) | 138 | 81 (13) | 15 | 10 (5) | 22 | 13 (13) |
| Cough | 3 | 3 (2) | 31 | 27 (4) | 5 | 4 (2) | 10 | 8 (8) |
| Dyspnea | 6 | 5 (3) | 24 | 15 (3) | 0 | 0 | 0 | 0 |
| Pharyngolaryngeal pain | 1 | 1 (<1) | 13 | 12 (2) | 3 | 3 (1) | 0 | 0 |
| Nasal congestion | 0 | 0 | 9 | 8 (1) | 3 | 2 (<1) | 3 | 3 (3) |
| Sinus congestion | 0 | 0 | 7 | 6 (<1) | 1 | 1 (<1) | 2 | 2 (2) |
| Epistaxis | 0 | 0 | 3 | 3 (<1) | 2 | 2 (<1) | 2 | 2 (2) |
| Asthma | 0 | 0 | 2 | 2 (<1) | 0 | 0 | 3 | 2 (2) |
| Injury, Poisoning and Procedural Complications | | | | | | | | |
| Any event | 13 | 11 (6) | 126 | 78 (13) | 14 | 9 (4) | 26 | 11 (11) |
| Fall | 4 | 4 (2) | 39 | 23 (4) | 4 | 4 (2) | 10 | 5 (5) |
| Contusion | 3 | 3 (2) | 14 | 12 (2) | 2 | 2 (<1) | 2 | 2 (2) |
| Back injury | 0 | 0 | 1 | 1 (<1) | 0 | 0 | 2 | 2 (2) |
| Vascular Disorders | | | | | | | | |
| Any event | 10 | 9 (5) | 97 | 74 (12) | 28 | 18 (9) | 5 | 5 (5) |
| Hypertension | 4 | 4 (2) | 20 | 19 (3) | 6 | 6 (3) | 3 | 3 (3) |
| Orthostatic hypotension | 2 | 2 (1) | 25 | 22 (4) | 9 | 5 (2) | 1 | 1 (<1) |
| Hypotension | 0 | 0 | 28 | 23 (4) | 8 | 6 (3) | 0 | 0 |
| Skin and Subcutaneous Tissue Disorders | | | | | | | | |
| Any event | 5 | 4 (2) | 78 | 55 (9) | 20 | 17 (8) | 14 | 11 (11) |
| Hyperhidrosis | 1 | 1 (<1) | 13 | 12 (2) | 3 | 3 (1) | 4 | 4 (4) |
| Rash | 2 | 1 (<1) | 10 | 9 (1) | 4 | 3 (1) | 4 | 3 (3) |
| Pruritus | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 2 | 2 (2) |
| Eye Disorders | | | | | | | | |
| Any event | 4 | 3 (2) | 72 | 45 (8) | 10 | 7 (3) | 7 | 6 (6) |
| Cataract | 2 | 1 (<1) | 7 | 6 (<1) | 0 | 0 | 4 | 4 (4) |
| Diplopia | 0 | 0 | 16 | 10 (2) | 0 | 0 | 1 | 1 (<1) |
| Metabolism and Nutrition Disorders | | | | | | | | |
| Any event | 6 | 6 (3) | 46 | 32 (5) | 6 | 6 (3) | 7 | 7 (7) |
| Decreased appetite | 1 | 1 (<1) | 3 | 3 (<1) | 0 | 0 | 2 | 2 (2) |
| Hypercholesterolemia | 0 | 0 | 2 | 2 (<1) | 0 | 0 | 2 | 2 (2) |
| Ear and Labyrinth Disorders | | | | | | | | |
| Any event | 12 | 7 (4) | 27 | 20 (3) | 9 | 5 (2) | 0 | 0 |
| Vertigo | 9 | 4 (2) | 21 | 14 (2) | 8 | 4 (2) | 0 | 0 |
| Reproductive System and Breast Disorders – Male Specific AEs | | | | | | | | |
| Any event | 2 | 2/129 (2) | 7 | 7/368 (2) | 2 | 2/119 (2) | 3 | 3/74 (4) |
| Erectile dysfunction | 1 | 1 (<1) | 6 | 6 (2) | 1 | 1 (<1) | 1 | 1 (1) |

Data Sources: Table 5.2 (# events), Table 5.1 (n [%]); Listing 5.4, Listing 5.5, ISS Listing 34 (Study 165), ISS Listing 35.1 (Study 167), 168 Listing 8.9, 169 Listing 8.1, 196 Listing 40, CSR 228 Listing 8.2

Abbreviations: CR = controlled-release; IR=immediate-release; N = total number of subjects; n = number of subjects; TEAE = treatment-emergent adverse event

Notes: TEAEs are ordered by decreasing incidence in the ropinirole CR group.

Subjects in the placebo group were all enrolled in Study 169; subjects in the pooled ropinirole CR group were enrolled in all studies in this study group; subjects in the pooled ropinirole IR group were enrolled in Studies 164, 165 and 168; and subjects in the Sinemet group were all enrolled in Study 228.

These TEAE data were analyzed for incidence (ie, percentage of total number of subjects reporting a given event [n [%]] and total number of events reported [# events] for a given TEAE.

1. AE data for Study 248 (n=133) are not reported here because in-house data available for this study at the time of this report included all SAEs, but only limited data for nonserious AEs unless the event led to withdrawal; therefore, the pooled ropinirole CR group here includes 613 of the 746 ropinirole CR-treated subjects for All PD Studies .
2. 'Any TEAE' refers to both non-gender- and gender-specific events with onset during any study period (excluding down-titration) regardless of potential relationship to study drug or intensity.

**Table 95 TEAEs Reported for ≥ 2% of Any Treatment Group *(Pooled Safety Population: All Controlled Phase 3* Adjunctive Therapy Studies [Studies 169 and 228])**

| System Organ Class<br>Preferred Term | Treatment Group by Dose Group (mg/day) at Onset of Event for *All Controlled Phase 3 Adjunctive Therapy Studies* (Studies 169 and 228)<br>Placebo N=191 | | Pooled Ropinirole CR N=306 | | Sinemet N=104 | |
|---|---|---|---|---|---|---|
| | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Any TEAE[1] | — | 104 (54) | — | 220 (72) | — | 86 (83) |
| Nervous System Disorders | | | | | | |
| Any event | — | 42 (22) | — | 107 (35) | — | 56 (53) |
| Dizziness | 7 | 6 (3) | 57 | 37 (12) | 16 | 15 (14) |
| Somnolence | 7 | 7 (4) | 34 | 27 (9) | 6 | 6 (6) |
| Dyskinesia | 7 | 5 (3) | 43 | 29 (9) | 2 | 2 (2) |
| Headache | 8 | 7 (4) | 17 | 14 (5) | 11 | 9 (9) |
| Tremor | 6 | 5 (3) | 9 | 8 (3) | 10 | 9 (9) |
| Balance disorder | 1 | 1 (<1) | 6 | 5 (2) | 0 | 0 |
| Gastrointestinal Disorders | | | | | | |
| Any event | — | 18 (9) | — | 89 (29) | — | 37 (36) |
| Nausea | 8 | 7 (4) | 54 | 49 (16) | 19 | 16 (15) |
| Constipation | 3 | 3 (2) | 16 | 15 (5) | 7 | 7 (7) |
| Diarrhea | 5 | 4 (2) | 14 | 14 (5) | 4 | 4 (4) |
| Vomiting | 4 | 3 (2) | 14 | 10 (3) | 2 | 2 (2) |
| Dyspepsia | 2 | 1 (<1) | 9 | 8 (3) | 4 | 4 (4) |
| Dry mouth | 1 | 1 (<1) | 8 | 8 (3) | 3 | 3 (3) |
| Abdominal pain | 1 | 1 (<1) | 6 | 6 (2) | 2 | 2 (2) |
| Abdominal pain upper | 1 | 1 (<1) | 2 | 2 (<1) | 4 | 3 (3) |
| Musculoskeletal and Connective Tissue Disorders | | | | | | |
| Any event | — | 25 (14) | — | 66 (22) | — | 32 (31) |
| Back pain | 5 | 4 (2) | 21 | 19 (6) | 12 | 10 (10) |
| Arthralgia | 3 | 3 (2) | 22 | 16 (5) | 10 | 9 (9) |
| Pain in extremity | 4 | 4 (2) | 14 | 14 (5) | 5 | 5 (5) |
| Muscle spasms | 1 | 1 (<1) | 10 | 8 (3) | 10 | 9 (9) |
| Shoulder pain | 2 | 2 (1) | 12 | 11 (4) | 1 | 1 (<1) |
| Myalgia | 3 | 3 (2) | 4 | 4 (1) | 1 | 1 (<1) |
| Musculoskeletal stiffness | 0 | 0 | 3 | 3 (<1) | 2 | 2 (2) |
| Neck pain | 0 | 0 | 2 | 2 (<1) | 3 | 3 (3) |
| Osteoarthritis | 3 | 3 (2) | 0 | 0 | 1 | 1 (<1) |
| Psychiatric Disorders | | | | | | |
| Any event | — | 28 (15) | — | 72 (24) | — | 23 (22) |
| Insomnia | 7 | 7 (4) | 25 | 24 (8) | 11 | 10 (10) |
| Depression | 5 | 5 (3) | 12 | 11 (4) | 6 | 6 (6) |
| Hallucination | 4 | 3 (2)[2] | 15 | 15 (5) | 0 | 0 |
| Edema peripheral | 2 | 2 (1) | 20 | 17 (6) | 1 | 1 (<1) |
| Anxiety | 2 | 2 (1) | 10 | 9 (3) | 4 | 4 (4) |
| Abnormal dreams | 4 | 4 (2) | 9 | 8 (3) | 2 | 2 (2) |
| Psychiatric Disorders (continued) | | | | | | |
| Hallucination, visual | 2 | 2 (1) | 5 | 10 (3) | 0 | 0 |
| Confusional state | 4 | 4 (2) | 0 | 0 | 3 | 3 (3) |
| Sleep disorder | 4 | 4 (2) | 3 | 3 (<1) | 0 | 0 |
| Nervousness | 0 | 0 | 1 | 1 (<1) | 2 | 2 (2) |
| Infections and Infestations | | | | | | |
| Any event | — | 12 (6) | — | 53 (17) | — | 24 (23) |
| Nasopharyngitis | 4 | 4 (2) | 16 | 13 (4) | 5 | 4 (4) |
| Sinusitis | 0 | 0 | 6 | 5 (2) | 3 | 3 (3) |
| General Disorders and Administration Site Conditions | | | | | | |
| Any event | — | 11 (6) | — | 52 (17) | — | 20 (19) |
| Fatigue | 4 | 3 (2) | 13 | 12 (4) | 10 | 9 (9) |
| Edema peripheral | 2 | 2 (1) | 20 | 17 (6) | 1 | 1 (<1) |
| Asthenia | 4 | 3 (2) | 6 | 6 (2) | 2 | 2 (2) |
| Chest pain | 0 | 0 | 9 | 6 (2) | 2 | 2 (2) |
| Feeling abnormal | 0 | 0 | 1 | 1 (<1) | 2 | 2 (2) |
| Injury, Poisoning and Procedural Complications | | | | | | |
| Any event | — | 9 (5) | — | 39 (13) | — | 10 (10) |
| Fall | 2 | 2 (1) | 12 | 11 (4) | 9 | 4 (4) |
| Contusion | 3 | 3 (2) | 3 | 3 (<1) | 2 | 2 (2) |
| Muscle strain | 0 | 0 | 3 | 3 (<1) | 3 | 2 (2) |
| Back injury | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Respiratory, Thoracic, Mediastinal | | | | | | |
| Any event | — | 10 (5) | — | 26 (8) | — | 13 (13) |
| Cough | 3 | 3 (2) | 11 | 10 (3) | 10 | 8 (8) |
| Dyspnea | 6 | 5 (3) | 6 | 10 (3) | 0 | 0 |
| Nasal congestion | 0 | 0 | 2 | 2 (<1) | 3 | 3 (3) |
| Sinus congestion | 0 | 0 | 2 | 2 (<1) | 2 | 2 (2) |
| Vascular Disorders | | | | | | |
| Any event | — | 9 (5) | — | 29 (9) | — | 6 (6) |
| Orthostatic hypotension | 2 | 2 (1) | 16 | 13 (4) | 1 | 1 (<1) |
| Hypertension | 4 | 4 (2) | 6 | 6 (2) | 3 | 3 (3) |
| Hypotension | 0 | 0 | 6 | 6 (2) | 0 | 0 |

**Table 95 (Continued) TEAEs Reported for ≥ 2% of Any Treatment Group *(Pooled Safety Population: All Controlled Phase 3* Adjunctive Therapy Studies [Studies 169 and 228])**

| System Organ Class<br>Preferred Term | Treatment Groups for *All Controlled Phase 3 Adjunctive Therapy Studies* (Studies 169 and 228)<br>Placebo N=191 | | Pooled Ropinirole CR N=306 | | Sinemet N=104 | |
|---|---|---|---|---|---|---|
| | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Skin and Subcutaneous Disorders | | | | | | |
| Any event | — | 4 (2) | — | 24 (8) | — | 10 (10) |
| Hyperhidrosis | 1 | 1 (<1) | 3 | 3 (<1) | 4 | 4 (4) |
| Rash | 2 | 1 (<1) | 4 | 4 (1) | 4 | 3 (3) |
| Pruritus | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Eye Disorders | | | | | | |
| Any event | — | 3 (2) | — | 24 (8) | — | 6 (6) |
| Diplopia | 0 | 0 | 11 | 7 (2) | 1 | 1 (<1) |
| Cataract | 2 | 1 (<1) | 5 | 4 (1) | 4 | 4 (4) |
| Metabolism and Nutrition Disorders | | | | | | |
| Any event | — | 5 (3) | — | 12 (4) | — | 7 (7) |
| Decreased appetite | 1 | 1 (<1) | 1 | 1 (<1) | 2 | 2 (2) |
| Hypercholesterolemia | 0 | 0 | 1 | 1 (<1) | 2 | 2 (2) |
| Ear and Labyrinth Disorders | | | | | | |
| Any event | — | 7 (4) | — | 10 (3) | — | 0 |
| Vertigo | 9 | 4 (2) | 11 | 8 (3) | 0 | 0 |
| Reproductive System and Breast Disorders – Male Specific | | | | | | |
| Any event | 2 | 2/129 (2) | 7 | 4/178 (2) | 3 | 3/74 (4) |
| Erectile dysfunction | 1 | 1 (<1) | 5 | 3 (2) | 1 | 1 (1) |

Data Sources: Table 5.95 (# events); Table 5.54 (n [%]); 169 Listing 8.1, CSR 228 Listing 8.2
Abbreviations: CR = controlled-release; N = total number of subjects; n = number of subjects; TEAE = treatment-emergent adverse event
Notes: TEAEs are ordered by decreasing incidence in the ropinirole CR group.
Subjects in the placebo group were all enrolled in Study 169; subjects in the pooled ropinirole CR group were enrolled in Studies 169 and 228; and subjects in the Sinemet group were all enrolled in Study 228.
These TEAE data were analyzed for incidence (ie, percentage of total number of subjects reporting a given event [n [%]] and total number of events reported [# events] for a given TEAE.

**Table 96 TEAEs Occurring for ≥ 2% of Either Treatment Group (Safety Population: Controlled Active Comparator Study [Adjunctive Therapy] [Study 228])**

| System Organ Class<br>Preferred Term | Treatment Groups for Controlled Adjunctive Therapy Study (Study 228)<br>Ropinirole CR N=104<br># Events | n (%) | Sinemet N=104<br># Events | n (%) |
|---|---|---|---|---|
| Any TEAE[1] | --- | 91 (88) | --- | 86 (83) |
| Nervous System Disorders, Any event | --- | 43 (41) | --- | 46 (44) |
| Dizziness | 34 | 21 (20) | 16 | 15 (14) |
| Somnolence | 15 | 13 (13) | 6 | 6 (6) |
| Headache | 8 | 7 (7) | 11 | 9 (9) |
| Tremor | 5 | 5 (5) | 10 | 9 (9) |
| Balance disorder | 6 | 5 (5) | 0 | 0 |
| Paresthesia | 2 | 2 (2) | 3 | 3 (3) |
| Dyskinesia | 2 | 2 (2) | 2 | 2 (2) |
| Amnesia | 3 | 2 (2) | 1 | 1 (<1) |
| Memory impairment | 2 | 2 (2) | 0 | 0 |
| Syncope | 2 | 2 (2) | 0 | 0 |
| Drooling | 2 | 2 (2) | 0 | 0 |
| Hypoesthesia | 1 | 1 (<1) | 2 | 2 (2) |
| Disturbance in attention | 0 | 0 | 2 | 2 (2) |
| Dizziness postural | 0 | 0 | 2 | 2 (2) |
| Poor quality sleep | 0 | 0 | 2 | 2 (2) |
| Gastrointestinal Disorders, Any event | --- | 44 (42) | --- | 37 (36) |
| Nausea | 30 | 26 (25) | 19 | 16 (15) |
| Constipation | 8 | 8 (8) | 7 | 7 (7) |
| Diarrhea | 7 | 7 (7) | 4 | 4 (4) |
| Dyspepsia | 6 | 5 (5) | 4 | 4 (4) |
| Vomiting | 8 | 5 (5) | 2 | 2 (2) |
| Dry mouth | 4 | 4 (4) | 3 | 3 (3) |
| Dysphagia | 4 | 4 (4) | 0 | 0 |
| Gastroesphogeal reflux disease | 3 | 3 (3) | 0 | 0 |
| Abdominal pain lower | 2 | 2 (2) | 0 | 0 |
| Flatulence | 2 | 2 (2) | 0 | 0 |
| Abdominal pain | 1 | 1 (<1) | 2 | 2 (2) |
| Abdominal pain upper | 0 | 0 | 4 | 3 (2) |
| Musculoskeletal and Connective Tissue Disorders, Any event | --- | 45 (43) | --- | 32 (31) |
| Back pain | 14 | 13 (13) | 12 | 10 (10) |
| Arthralgia | 17 | 13 (13) | 10 | 9 (9) |
| Muscle spasms | 9 | 7 (7) | 10 | 9 (9) |
| Pain in extremity | 10 | 10 (10) | 6 | 5 (5) |
| Shoulder pain | 10 | 9 (9) | 2 | 1 (<1) |
| Musculoskeletal stiffness | 3 | 3 (3) | 2 | 2 (2) |
| Neck pain | 2 | 2 (2) | 3 | 3 (3) |
| Arthritis | 2 | 2 (2) | 2 | 1 (<1) |
| Myalgia | 2 | 2 (2) | 1 | 1 (<1) |
| Flank pain | 2 | 2 (2) | 0 | 0 |
| Intervertral disc protrusion | 2 | 2 (2) | 0 | 0 |
| Psychiatric Disorders, Any event | --- | 33 (32) | --- | 23 (22) |
| Insomnia | 17 | 17 (16) | 11 | 10 (10) |
| Depression | 6 | 6 (6) | 6 | 6 (6) |
| Anxiety | 5 | 4 (4) | 4 | 4 (4) |
| Abnormal dreams | 4 | 3 (3) | 2 | 2 (2) |
| Hallucination | 4 | 4 (4) | 0 | 0 |
| Nightmare | 2 | 2 (2) | 1 | 1 (<1) |
| Libido increased | 2 | 2 (2) | 0 | 0 |
| Confusional state | 0 | 0 | 3 | 3 (3) |
| Nervousness | 0 | 0 | 2 | 2 (2) |
| Infections and Infestations, Any event | --- | 31 (30) | --- | 24 (23) |
| Upper respiratory tract infection | 8 | 6 (6) | 7 | 7 (7) |
| Nasopharyngitis | 8 | 8 (8) | 6 | 4 (4) |
| Sinusitis | 4 | 4 (4) | 3 | 3 (3) |
| Urinary tract infection | 2 | 2 (2) | 2 | 1 (<1) |
| Gastroenteritis | 2 | 2 (2) | 0 | 0 |
| Influenza | 2 | 2 (2) | 0 | 0 |
| Herpes simplex | 2 | 2 (2) | 0 | 0 |
| General Disorders and Administration Site Conditions, Any event | --- | 27 (26) | --- | 20 (19) |
| Fatigue | 10 | 10 (10) | 10 | 9 (9) |
| Edema peripheral | 11 | 9 (9) | 1 | 1 (<1) |
| Asthenia | 3 | 3 (3) | 2 | 2 (2) |
| Chest pain | 3 | 3 (3) | 2 | 2 (2) |
| Feeling abnormal | 0 | 0 | 2 | 2 (2) |

**Table 96 (Continued) TEAEs Occurring for ≥ 2% of Either Treatment Group (Safety Population: Controlled Active Comparator Study [Adjunctive Therapy] [Study 228])**

| System Organ Class<br>Preferred Term | Treatment Groups for Controlled Adjunctive Therapy (Study 228)<br>Ropinirole CR N=104<br># Events | n (%) | Sinemet N=104<br># Events | n (%) |
|---|---|---|---|---|
| Respiratory, Thoracic and Mediastinal Disorders, Any event | — | 20 (19) | — | 13 (13) |
| Cough | 10 | 9 (9) | 10 | 8 (8) |
| Chronic obstructive pulmonary disease | 2 | 2 (2) | 0 | 0 |
| Nasal congestion | 1 | 1 (<1) | 3 | 3 (3) |
| Sinus congestion | 1 | 1 (<1) | 2 | 2 (2) |
| Asthma | 0 | 0 | 3 | 2 (2) |
| Injury, Poisoning and Procedural Complications, Any event | — | 21 (20) | — | 10 (10) |
| Fall | 7 | 6 (6) | 9 | 4 (4) |
| Contusion | 2 | 2 (2) | 3 | 2 (2) |
| Excoriation | 2 | 2 (2) | 4 | 1 (<1) |
| Wound | 2 | 2 (2) | 0 | 0 |
| Stress fracture | 2 | 2 (2) | 0 | 0 |
| Muscle strain | 1 | 1 (<1) | 3 | 2 (2) |
| Skin and Subcutaneous Tissue Disorders, Any event | — | 14 (13) | — | 10 (10) |
| Hyperhidrosis | 2 | 2 (2) | 4 | 4 (4) |
| Rash | 2 | 2 (2) | 4 | 3 (3) |
| Ecchymosis | 2 | 2 (2) | 0 | 0 |
| Swelling face | 2 | 2 (2) | 0 | 0 |
| Eye Disorders, Any event | — | 13 (13) | — | 6 (6) |
| Diplopia | 5 | 5 (5) | 1 | 1 (<1) |
| Cataract | 1 | 1 (<1) | 4 | 4 (4) |
| Metabolism and Nutrition Disorders, Any event | — | 7 (7) | — | 7 (7) |
| Anorexia | 3 | 3 (3) | 1 | 1 (<1) |
| Decrease appetite | 1 | 1 (<1) | 2 | 2 (2) |
| Hyperlipidemia | 1 | 1 (<1) | 2 | 2 (2) |
| Vascular Disorders, Any event | — | 8 (8) | — | 6 (6) |
| Orthostatic hypotension | 3 | 3 (3) | 1 | 1 (<1) |
| Flushing | 2 | 2 (2) | 0 | 0 |
| Hypertension | 0 | 0 | 3 | 3 (3) |
| Investigations, Any event | — | 8 (8) | — | 4 (4) |
| Blood pressure increased[1] | 4 | 3 (3) | 0 | 0 |
| Weight increased | 2 | 2 (2) | 0 | 0 |
| Cardiac Disorders, Any event | — | 6 (6) | — | 5 (5) |
| Acute coronary syndrome | 2 | 2 (2) | 0 | 0 |
| Reproductive System and Breast Disorders (Male Specific), Any event | — | 3/60 (5) | — | 3/74 (4) |
| Erectile dysfunction | 2 | 2/60 (3) | 1 | 1/74 (1) |
| Erection increased | 1 | 1/60 (2) | 0 | 0/74 |

Data Sources: Table 5.67 (# events); Table 5.38 [n (%)]; CSR 228 Listing 6.2
Abbreviations: CR = controlled-release; N = total number of subjects; n = number of subjects; TEAE = treatment-emergent adverse event
Note: TEAE data were analyzed for incidence [ie, percentage of total number of subjects reporting a given event [n (%)] and total number of events reported (# events)] for a given TEAE.
1. 'Any TEAE' refers to both non-gender- and gender-specific events with onset during any study period (excluding down-titration) regardless of potential relationship to study drug or intensity.



Table 97 shows the frequency of relatively common TEAEs (≥ 2 %) observed during the whole study period in study 168 comparing treatment of ropinirole ER vs IR. In general, the nature and frequency of TEAEs is quite similar.

**Table 97 TEAEs Occurring for ≥ 2% of Either Treatment Group (Safety Population: Controlled Active- Comparator Study [Monotherapy] [Study 168])**

| System Organ Class<br>Preferred Term | Treatment Group for Controlled Active-Comparator Study (Adjunctive Therapy) (Study 169) | | | |
|---|---|---|---|---|
| | Ropinirole CR N=140 | | Ropinirole IR N=149 | |
| | # Events | n (%) | # Events | n (%) |
| Any TEAE[1] | — | 76 (54) | — | 84 (56) |
| Gastrointestinal Disorders, Any event | — | 43 (31) | — | 45 (30) |
| Nausea | 50 | 27 (19) | 53 | 30 (20) |
| Constipation | 8 | 7 (5) | 9 | 7 (5) |
| Vomiting | 6 | 5 (4) | 4 | 4 (3) |
| Dyspepsia | 4 | 4 (3) | 12 | 10 (7) |
| Diarrhea | 3 | 3 (2) | 3 | 3 (2) |
| Flatulence | 6 | 3 (2) | 2 | 2 (1) |
| Abdominal pain | 4 | 3 (2) | 1 | 1 (<1) |
| Nervous System Disorders, Any event | — | 34 (24) | — | 45 (30) |
| Somnolence | 21 | 16 (11) | 30 | 22 (15) |
| Dizziness | 11 | 9 (6) | 13 | 9 (6) |
| Headache | 20 | 8 (6) | 10 | 8 (5) |
| Syncope | 1 | 1 (<1) | 6 | 5 (3) |
| Lethargy | 1 | 1 (<1) | 4 | 3 (2) |
| Tremor | 1 | 1 (<1) | 3 | 3 (2) |
| Infections and Infestations, Any event | — | 13 (9) | — | 19 (13) |
| Nasopharyngitis | 2 | 2 (1) | 7 | 6 (4) |
| Urinary tract infection | 4 | 3 (2) | 3 | 3 (2) |
| Influenza | 3 | 2 (1) | 3 | 3 (2) |
| Musculoskeletal and Connective Tissue Disorders, Any event | — | 22 (16) | — | 17 (11) |
| Back pain | 4 | 4 (3) | 3 | 3 (2) |
| Muscle spasms | 4 | 4 (3) | 3 | 3 (2) |
| Myalgia | 5 | 5 (4) | 1 | 1 (<1) |
| Pain in extremity | 3 | 3 (2) | 1 | 1 (<1) |
| Psychiatric Disorders, Any event | — | 20 (14) | — | 16 (11) |
| Insomnia | 8 | 4 (3) | 6 | 5 (3) |
| Depression | 3 | 3 (2) | 6 | 5 (3) |
| Anxiety | 5 | 4 (3) | 3 | 2 (1) |
| Sleep disorder | 5 | 5 (4) | 1 | 1 (<1) |
| Hallucination | 5 | 4 (3) | 1 | 1 (<1) |
| Hallucination, visual | 5 | 3 (2) | 2 | 2 (1) |
| General Disorders and Administration Site Conditions, Any event | — | 11 (8) | — | 14 (9) |
| Fatigue | 4 | 4 (3) | 8 | 8 (5) |
| Edema peripheral | 3 | 3 (2) | 3 | 2 (1) |
| Vascular Disorders, Any event | — | 6 (4) | — | 11 (7) |
| Hypertension | 4 | 4 (3) | 7 | 5 (3) |
| Orthostatic hypotension | 0 | 0 | 8 | 4 (3) |
| Injury, Poisoning and Procedural Complications, Any event | — | 8 (6) | — | 8 (5) |
| Contusion | 3 | 3 (2) | 2 | 2 (1) |
| Fall | 4 | 2 (1) | 3 | 3 (2) |
| Respiratory, Thoracic and Mediastinal Disorders, Any event | — | 9 (6) | — | 7 (5) |
| Pharyngolaryngeal pain | 1 | 1 (<1) | 3 | 3 (2) |
| Cardiac Disorders, Any event | — | 4 (3) | — | 6 (4) |
| Angina pectoris | 0 | 0 | 3 | 3 (2) |
| Ear and Labyrinth Disorders, Any event | — | 5 (4) | — | 3 (2) |
| Vertigo | 7 | 4 (3) | 4 | 3 (2) |
| Balance disorder | 1 | 1 (<1) | 2 | 3 (2) |

Data Sources: Table 5.7.1 (# events); Table 5.6 (n [%]); 168 Listing 8.9

Abbreviations: CR = controlled-release; IR=immediate-release; N = total number of subjects; n = number of subjects; TEAE = treatment-emergent adverse event

Note: For this analysis, both incidence (ie, percentage of total number of subjects reporting a given event [n [%]]) and total number of events reported (# events) were determined for each TEAE.

7.1.5.4 Common adverse event tables

- See above section 7.1.5.3 for common adverse event tables.

7.1.5.5 Identifying common and drug-related adverse events

In an effort to determine the adverse drug reactions (ADRs) for ropinirole CR in Parkinson's Disease , all TEAEs were assessed based on the FDA guidance. Decisions on whether to categorize an AE as an ADR were based on clinical judgment and factors that included the frequency of reporting of the TEAE, whether the TEAE rate was more common in the ropinirole CR group than in the placebo group during the treatment period, the extent of a dose-response relationship where multiple doses were assessed, the extent to which the TEAE was consistent with the pharmacology of the drug, and other factors such as whether the TEAE is known to be caused by related drugs and whether or not the TEAE caused withdrawal from study. All TEAE listings were also reviewed to identify any individual events considered indicative of atypical 'drug-related' reactions for other drugs (e.g., Stevens-Johnson Syndrome, drug hypersensitivity, blood dyscrasia); however, none were identified.

The sponsor presented analyses (in individual studies and in various pools of studies) occurring with an incidence of $\geq$ 2 % for TEAEs considered to be drug-related. The most common TEAEs were principally consistent with dopaminergic therapy including dyskinesia, nausea, somnolence, dizziness, hallucination and orthostatic hypotension; these had higher incidence in the ropinirole CR group.

**Reviewer Comment**

- It is noteworthy that many of the TEAEs judged to be "drug-related" in the various tabular analyses and noted above as the most common TEAEs characterized as such were similar to those TEAEs that my treatment difference/effect analyses suggested were treatment-related simply because the incidence for ER ropinirole was greater than that for placebo.

7.1.5.6 Additional analyses and explorations

In response to requests from the DNP the sponsor conducted and submitted additional analyses of TEAEs (serious and non-serious TEAEs, serious TEAEs – SAEs, and TEAEs causing study discontinuation) showing the frequency (e.g. incidence) of TEAEs with the their onset during the titration phase, during the maintenance phase, during the titration phase and persisting ($\geq$ 7 days) into the maintenance phase compared to TEAEs with their onset during any time/phase in the study.

The sponsor also analyzed all these requested, additional analyses with respect to treatment and ER ropinirole dose ($\leq$ 8 mg/day, > 8 – 16 mg/day, > 16 – 24 mg/day, and "any" dose day).

The sponsor presented Table 98 that showed the incidence of TEAEs (≥ 2%) of patients by the Preferred Term (PT) in the titration period, in the maintenance period, and persisting from titration period into the maintenance period in the randomized, double-blind, placebo-controlled Study 169 in advanced Parkinson's Disease.

Based upon data analyses shown in Table 98, I have constructed a table (Table 99) that shows the treatment difference/effect (ER ropinirole % > placebo %) for various analyses of TEAEs occurring ≥ 2 % of patients treated with ER ropinirole in Study 169. These analyses were for TEAEs developing during the whole study period, during the titration phase, during the maintenance phase, and during the titration phase and persisting (≥ 7 days) into the maintenance phase.

**Table 98 TEAEs in ≥ 2% of Patients by Preferred Term in Titration Period, in Maintenance Period, or Persisting from Iitration into Maintenance Period in Study 169**

| Study Period at Onset / Preferred Term | Treatment Group by Dose Group (mg/day) at Onset of Event for Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo N=181 | | | | | | | | Ropinirole CR N=202 | | | | | | | |
| Treated during Titration, a | 181 | | 178 | | 114 | | 181 | | 202 | | 169 | | 167 | | 202 | |
| | ≤8 | | >8 to ≤18 | | >18 | | Any Dose | | ≤8 | | >8 to ≤18 | | >18 | | Any Dose | |
| Onset during Titration | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Dyskinesia | 0 | 0 | 2 | 2 (1) | 0 | 0 | 2 | 2 (1) | 11 | 10 (5) | 11 | 11 (7) | 2 | 2 (1) | 24 | 20 (10) |
| Nausea | 2 | 2 (1) | 3 | 3 (2) | 1 | 1 (<1) | 6 | 5 (3) | 19 | 15 (7) | 3 | 3 (2) | 2 | 2 (1) | 23 | 17 (8) |
| Dizziness | 3 | 2 (1) | 2 | 2 (1) | 1 | 1 (<1) | 6 | 5 (3) | 21 | 10 (5) | 5 | 3 (2) | 1 | 1 (<1) | 27 | 11 (5) |
| Somnolence | 5 | 5 (3) | 0 | 0 | 0 | 0 | 5 | 5 (3) | 10 | 7 (3) | 2 | 2 (1) | 0 | 0 | 12 | 9 (4) |
| Orthostatic hypotension | 1 | 1 (<1) | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 8 | 6 (3) | 1 | 1 (<1) | 0 | 0 | 9 | 7 (3) |
| Edema peripheral | 1 | 1 (<1) | 1 | 1 (<1) | 0 | 0 | 2 | 2 (1) | 4 | 4 (2) | 0 | 0 | 2 | 2 (1) | 6 | 6 (3) |
| Vertigo | 0 | 0 | 2 | 2 (1) | 0 | 0 | 2 | 2 (1) | 5 | 4 (2) | 1 | 1 (<1) | 1 | 1 (<1) | 7 | 6 (3) |
| Constipation | 2 | 2 (1) | 1 | 1 (<1) | 0 | 0 | 3 | 3 (2) | 5 | 5 (2) | 0 | 0 | 0 | 0 | 5 | 5 (2) |
| Hypotension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 4 (2) | 1 | 1 (<1) | 1 | 1 (<1) | 6 | 5 (2) |
| Insomnia | 4 | 4 (2) | 1 | 1 (<1) | 0 | 0 | 5 | 5 (3) | 4 | 4 (2) | 0 | 0 | 1 | 1 (<1) | 5 | 5 (2) |
| Back pain | 2 | 1 (<1) | 0 | 0 | 1 | 1 (<1) | 3 | 2 (1) | 3 | 3 (1) | 1 | 1 (<1) | 0 | 0 | 4 | 4 (2) |
| Dry mouth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 (1) | 1 | 1 (<1) | 0 | 0 | 4 | 4 (2) |
| Headache | 4 | 3 (2) | 1 | 1 (<1) | 0 | 0 | 5 | 4 (2) | 4 | 4 (2) | 0 | 0 | 0 | 0 | 4 | 4 (2) |
| Diarrhea | 3 | 3 (2) | 1 | 1 (<1) | 0 | 0 | 4 | 4 (2) | 2 | 2 (<1) | 0 | 0 | 1 | 1 (<1) | 3 | 3 (1) |
| Tremor | 3 | 2 (1) | 1 | 1 (<1) | 2 | 2 (2) | 6 | 4 (2) | 2 | 2 (<1) | 0 | 0 | 1 | 1 (<1) | 3 | 2 (<1) |
| Abnormal dreams | 3 | 3 (2) | 1 | 1 (<1) | 0 | 0 | 4 | 4 (2) | 1 | 1 (<1) | 0 | 0 | 1 | 1 (<1) | 2 | 2 (<1) |
| Arthralgia | 2 | 2 (1) | 0 | 0 | 1 | 1 (<1) | 3 | 3 (2) | 3 | 2 (<1) | 0 | 0 | 0 | 0 | 3 | 2 (<1) |
| Hypertension | 4 | 4 (2) | 0 | 0 | 0 | 0 | 4 | 4 (2) | 2 | 2 (<1) | 0 | 0 | 0 | 0 | 2 | 2 (<1) |
| Joint swelling | 1 | 2 (1) | 2 | 2 (1) | 0 | 0 | 3 | 3 (2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Parkinson's disease | 2 | 1 (<1) | 1 | 1 (<1) | 2 | 1 (<1) | 4 | 3 (2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Onset during Maintenance | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Dyskinesia | 0 | 0 | 3 | 2 (1) | 2 | 1 (<1) | 5 | 3 (2) | 1 | 1 (1) | 6 | 5 (3) | 10 | 8 (5) | 17 | 13 (6) |
| Hallucination | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) | 1 | 1 (1) | 3 | 3 (2) | 4 | 4 (2) | 8 | 8 (4) |
| Nausea | 0 | 0 | 1 | 1 (1) | 1 | 1 (<1) | 2 | 2 (1) | 0 | 0 | 5 | 4 (2) | 5 | 3 (2) | 10 | 7 (3) |
| Dizziness | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) | 0 | 0 | 2 | 2 (1) | 4 | 4 (2) | 6 | 6 (3) |
| Somnolence | 0 | 0 | 0 | 0 | 2 | 2 (2) | 2 | 2 (1) | 2 | 2 (1) | 1 | 1 (1) | 4 | 3 (2) | 7 | 6 (3) |
| Anxiety | 0 | 0 | 1 | 1 (1) | 1 | 1 (<1) | 2 | 2 (1) | 1 | 1 (1) | 1 | 1 (1) | 2 | 2 (1) | 4 | 4 (2) |
| Orthostatic hypotension | 0 | 0 | 1 | 1 (1) | 0 | 0 | 1 | 1 (<1) | 0 | 0 | 3 | 3 (2) | 1 | 1 (<1) | 4 | 4 (2) |
| Diarrhea | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) | 1 | 1 (1) | 1 | 1 (1) | 2 | 2 (1) | 4 | 4 (2) |
| Hypertension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 (1) | 1 | 1 (1) | 2 | 2 (1) | 4 | 4 (2) |
| Vertigo | 0 | 0 | 4 | 1 (1) | 3 | 2 (2) | 7 | 3 (2) | 1 | 1 (1) | 2 | 2 (1) | 1 | 1 (<1) | 4 | 4 (2) |
| Abnormal dreams | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (1) | 1 | 1 (1) | 0 | 0 | 3 | 3 (1) |
| Back pain | 0 | 0 | 1 | 1 (1) | 1 | 1 (<1) | 2 | 2 (1) | 1 | 1 (1) | 1 | 1 (1) | 1 | 1 (<1) | 3 | 3 (1) |
| Cataract | 0 | 0 | 1 | 1 (1) | 0 | 0 | 1 | 1 (<1) | 1 | 1 (1) | 1 | 1 (1) | 1 | 1 (<1) | 3 | 3 (1) |
| Chest pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 (1) | 0 | 0 | 2 | 2 (1) | 5 | 3 (1) |
| Constipation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (1) | 1 | 1 (<1) | 3 | 3 (1) |
| Depression | 0 | 0 | 1 | 1 (1) | 3 | 3 (2) | 4 | 4 (2) | 1 | 1 (1) | 1 | 1 (1) | 1 | 1 (<1) | 3 | 3 (1) |
| Fall | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 (2) | 3 | 3 (1) |
| Hallucination, visual | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) | 2 | 1 (1) | 3 | 2 (1) | 0 | 0 | 5 | 3 (1) |
| Headache | 0 | 0 | 1 | 1 (1) | 2 | 2 (2) | 3 | 3 (2) | 1 | 1 (1) | 1 | 1 (1) | 3 | 1 (<1) | 5 | 3 (1) |
| Insomnia | 0 | 0 | 1 | 1 (1) | 1 | 1 (<1) | 2 | 2 (1) | 0 | 0 | 1 | 1 (1) | 2 | 2 (1) | 3 | 3 (1) |
| Pain in extremity | 0 | 0 | 1 | 1 (1) | 0 | 0 | 1 | 1 (<1) | 0 | 0 | 0 | 0 | 3 | 3 (2) | 3 | 3 (1) |
| Vomiting | 0 | 0 | 1 | 1 (1) | 0 | 0 | 1 | 1 (<1) | 0 | 0 | 3 | 3 (2) | 0 | 0 | 3 | 3 (1) |
| Dyspnea | 1 | 1 (0) | 2 | 2 (1) | 1 | 1 (<1) | 4 | 4 (2) | 0 | 0 | 0 | 0 | 2 | 2 (1) | 2 | 2 (1) |
| Nasopharyngitis | 0 | 0 | 1 | 1 (1) | 1 | 1 (<1) | 2 | 2 (1) | 0 | 0 | 4 | 4 (2) | 1 | 1 (<1) | 5 | 5 (2) |
| Sleep disorder | 0 | 0 | 0 | 0 | 3 | 3 (2) | 3 | 3 (2) | 0 | 0 | 0 | 0 | 2 | 2 (1) | 2 | 2 (1) |
| Urinary tract infection | 0 | 0 | 1 | 1 (1) | 1 | 1 (<1) | 2 | 2 (1) | 1 | 1 (1) | 1 | 1 (1) | 1 | 1 (<1) | 3 | 3 (1) |
| Parkinson's disease | 0 | 0 | 0 | 0 | 3 | 3 (2) | 3 | 3 (2) | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) |
| Bronchitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 (1) | 1 | 1 (1) | 1 | 1 (<1) | 3 | 3 (1) |
| Onset during Titration, Persists into Maintenance | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Dyskinesia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 (2) | 3 | 3 (2) | 1 | 1 (<1) | 7 | 7 (4) |
| Dizziness | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) | 2 | 2 (1) | 2 | 2 (1) | 1 | 1 (<1) | 5 | 4 (2) |
| Nausea | 0 | 0 | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) | 1 | 1 (<1) | 3 | 2 (1) | 1 | 1 (<1) | 4 | 4 (2) |
| Orthostatic hypotension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 4 (2) | 0 | 0 | 0 | 0 | 4 | 4 (2) |
| Dry mouth | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (1) | 1 | 1 (<1) | 0 | 0 | 3 | 3 (1) |
| Edema peripheral | 0 | 0 | | 1 (<1) | 0 | 0 | 1 | 1 (<1) | 1 | 1 (<1) | 0 | 0 | 2 | 2 (1) | 3 | 3 (1) |

Data Sources: Table 5.83 (# events), Table 5.23 (n (%)) (Titration); Table 5.91 (# events), Table 5.24 (n (%)) (Maintenance Phase); Table 5.92 (# events), Table 5.25 (n (%)) (Persisting into Maintenance); 169 Listing 8.1

Abbreviations: CR=controlled-release; N = total number of subjects; n = number of subjects; TEAE=treatment-emergent adverse event

Notes: Events are ordered by decreasing incidence in the ropinirole CR group.

1. "Any TEAE" includes both non-gender and gender specific events.

**Table 99 TEAEs ( ER ropinirole ≥ 2 % and > Placebo % )with Onset In Any Phase, In the Titration Phase, In the Maintenance Phase, and Onset in the Titration Phase Persisting into the Maintenance Phase in Study 169 (Advanced Parkinson's Disease, Adjunctive Treatment)**

| TEAE (PT) | Any Study Time | | | Titration Phase | | | Maintenance Phase | | | "Persistent" from Titration Phase into Maintenance Phase | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | P | ER-R | TE | P | ER-R | TE | P | ER-R | TE | P | ER-R | TE |
| Dyskinesia* | 3 | 13 | 10 | 1 | 10 | 9 | 2 | 7 | 5 | 0 | 4 | 4 |
| Dizziness | 3 | 8 | 5 | 3 | 5 | 2 | < 1 | 3 | > 2 | < 1 | 2 | > 1 |
| Somnolence | 3 | 7 | 4 | 3 | 4 | 1 | 1 | 3 | 2 | | | |
| Anxiety | 1 | 2 | 1 | | | | 1 | 2 | 1 | | | |
| Hallucination | 3 | 7 | 4 | 2 | 3 | 1 | 0 | 2 | 2 | 0 | 2 | 2 |
| Insomnia | | | | | | | 1 | 2 | 1 | | | |
| Abnormal dreams | | | | | | | 0 | 2 | 2 | | | |
| Nausea | 4 | 11 | 7 | 3 | 8 | 5 | 1 | 4 | 3 | < 1 | 2 | > 1 |
| Vomiting | | | | | | | <1 | 2 | >1 | | | |
| Diarrhea | 2 | 3 | 1 | | | | <1 | 2 | >1 | | | |
| Constipation | 2 | 4 | 2 | | | | 0 | 2 | 2 | | | |
| Abdominal pain/discomfort | 3 | 6 | 3 | 2 | 5 | 3 | <1 | 2 | >1 | <1 | 2 | >1 |
| Dry mouth | < 1 | 2 | > 1 | 0 | 2 | 2 | | | | 0 | 2 | 2 |
| Back pain | 2 | 3 | 1 | | | | 1 | 2 | 1 | | | |
| Pain in extremity | | | | | | | < 1 | 2 | > 1 | | | |
| Peripheral edema | 1 | 4 | 3 | 1 | 3 | 2 | | | | < 1 | 2 | > 1 |
| Orthostatic hypotension | 1 | 5 | 4 | < 1 | 3 | > 2 | < 1 | 2 | > 1 | 0 | 2 | 2 |
| Hypertension* | 2 | 3 | 1 | 0 | 2 | 2 | 0 | 2 | 2 | | | |
| Hypotension | 0 | 2 | 2 | | | | | | | | | |
| Fall* | 1 | 2 | 1 | | | | 0 | 2 | 2 | | | |
| Vertigo | 2 | 4 | 2 | 1 | 3 | 2 | | | | | | |
| Nasopharyngitis | | | | | | | 1 | 3 | 2 | | | |
| Urinary tract infection | | | | | | | 1 | 2 | 1 | | | |
| Bronchitis | | | | | | | 0 | 2 | 2 | | | |
| Chest pain | | | | | | | 0 | 2 | 2 | | | |
| Cataract | | | | | | | < 1 | 2 | > 1 | | | |

*Dose-related at any time in study

The risk for many TEAEs with REQUIP XL treatment was particularly increased in either the titration or maintenance phases of the study. I will point out the TEAEs in these various analyses in which the treatment difference/effect for ER ropinirole was at least 2 %. During the whole study period, an increased risk (shown in descending order of % treatment difference and for a treatment difference/effect of at least 2 %) was observed

for dyskinesia, nausea, hallucination, dizziness, vertigo, hypertension, peripheral edema, and dry mouth. During the titration phase, an increased risk (shown in descending order of % treatment difference and for a treatment difference/effect of at least 2 %) was observed for dyskinesia, nausea, hallucination, dizziness, vertigo, hypertension, peripheral edema, and dry mouth. During the maintenance phase, an increased risk was observed for dyskinesia, hallucination, nausea, dizziness, somnolence, fall, hypertension, abnormal dreams, , ,constipation, chest pain, and bronchitis. Some adverse reactions developing in the titration phase persisted ($\geq$ 7 days) into the maintenance phase. These "persistent" adverse reactions included dyskinesia, hallucination, orthostatic hypotension, and dry mouth.

There were no TEAEs that were unique for an increased risk as occurring only in the titration period. However, some TEAEs only showed an increased incidence risk only in the maintenance phase : urinary tract infection, nasopharyngitis, bronchitis, chest pain, cataract, pain in extremity, insomnia, abnormal dreams, and vomiting. Of interest, several TEAEs (i.e. dyskinesia, dizziness, hallucination, nausea, abdominal pain/discomfort, and orthostatic hypotension) that clearly seemed ER ropinirole-related showed an increased incidence risk in all 4 analyses.

Similar analyses of study 228 separately and of pooled data from the 2 advanced Parkinson's Disease studies (169 and 228) suggested generally similar increased risks for certain TEAEs as were suggested by analyses of study 169.

The sponsor also conducted and presented similar analyses for study 168 comparing treatment with ropinirole ER with IR. Table 100 shows the incidence of TEAEs developing in the titration phase, in the maintenance phase, and persisting into the maintenance phase after onset in the titration phase.

**Table 100 TEAEs in ≥ 2% of Patients by Preferred Term in Titration Period, in Maintenance Period, or Persisting from Iitration into Maintenance Period in Study 168**

| Study Period at Onset / Preferred Term | Treatment Groups for Controlled Active-Comparator Study (Monotherapy) (Study 168) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ropinirole CR N=143 | | | | | | | | Ropinirole IR N=148 | | | | | | | |
| | ≤8 | | >8 to ≤18 | | >18 | | Any Dose | | ≤8 | | >8 to ≤18 | | >18 | | Any Dose | |
| Treated during Titration, n | 122 | | 84 | | 54 | | 140 | | 93 | | 81 | | 48 | | 146 | |
| Onset during Titration | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Nausea | 22 | 15 (20) | 5 | 6 (9) | 4 | 3 (7) | 32 | 21 (23) | 34 | 21 (24) | 3 | 3 (8) | 0 | 0 | 37 | 22 (26) |
| Somnolence | 6 | 6 (8) | 3 | 3 (4) | 0 | 0 | 9 | 8 (11) | 12 | 12 (14) | 1 | 1 (3) | 0 | 0 | 13 | 12 (14) |
| Dizziness | 4 | 3 (4) | 2 | 2 (3) | 1 | 1 (2) | 7 | 6 (8) | 8 | 7 (8) | 1 | 1 (3) | 0 | 0 | 9 | 8 (9) |
| Dyspepsia | 1 | 1 (1) | 2 | 2 (3) | 1 | 1 (2) | 4 | 4 (5) | 6 | 6 (7) | 0 | 0 | 0 | 0 | 6 | 6 (7) |
| Headache | 8 | 5 (7) | 1 | 1 (1) | 2 | 2 (4) | 11 | 6 (8) | 5 | 5 (6) | 0 | | 0 | 0 | 5 | 5 (6) |
| Fatigue | 2 | 2 (3) | 0 | 0 | 0 | 0 | 3 | 3 (4) | 5 | 5 (6) | 0 | 0 | 0 | 0 | 5 | 5 (6) |
| Nasopharyngitis | 0 | 0 | 0 | 0 | 2 | 2 (4) | 2 | 2 (3) | 4 | 4 (5) | 1 | 1 (3) | 0 | 0 | 5 | 5 (6) |
| Constipation | 3 | 3 (4) | 0 | 0 | 1 | 1 (2) | 4 | 4 (5) | 5 | 4 (5) | 0 | 0 | 0 | 0 | 5 | 4 (5) |
| Confusion | 0 | 0 | 1 | 1 (1) | 2 | 2 (4) | 3 | 3 (4) | 1 | 1 (1) | 0 | 2 (6) | 0 | 0 | 1 | 4 (5) |
| Hypertension | 2 | 2 (3) | 0 | 0 | 0 | 0 | 2 | 2 (3) | 4 | 2 (2) | 2 | 2 (6) | 0 | 0 | 6 | 4 (5) |
| Insomnia | 0 | 0 | 1 | 1 (1) | 2 | 2 (4) | 3 | 3 (3) | 5 | 4 (5) | 0 | 0 | 0 | 0 | 5 | 4 (5) |
| Syncope | 0 | 0 | 1 | 1 (1) | 0 | 0 | 1 | 1 (1) | 5 | 4 (5) | 0 | 0 | 0 | 0 | 5 | 4 (5) |
| Lethargy | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) | 4 | 3 (3) | 0 | 0 | 0 | 0 | 4 | 3 (3) |
| Orthostatic hypotension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 3 (3) | 0 | 0 | 0 | 0 | 4 | 3 (3) |
| URI | 1 | 1 (1) | 0 | 0 | 0 | 1 (2) | 1 | 2 (3) | 0 | 3 (3) | 0 | 0 | 0 | 0 | 0 | 0 |
| Cough | 1 | 1 (1) | 1 | 1 (1) | 0 | 0 | 2 | 2 (3) | 2 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Diarrhea | 1 | 1 (1) | 2 | 2 (3) | 0 | 0 | 3 | 3 (4) | 2 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Erectile dysfunction[2] | 0 | 0/48 | 0 | 0/43 | 0 | 0/30 | 0 | 0/48 | 1 | 1/43 (2) | 0 | 0/27 | 0 | 0 | 1 | 1/43 (2) |
| Hypotension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Influenza | 1 | 1 (1) | 1 | 1 (1) | 0 | 0 | 2 | 2 (3) | 2 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Pruritis[2] | 0 | 0/48 | 0 | 0/43 | 0 | 0/30 | 0 | 0/48 | 1 | 1/43 (2) | 0 | 0/27 | 0 | 0 | 1 | 1/43 (2) |
| Tremor | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Viral infection | 1 | 1 (1) | 0 | 0 | 1 | 1 (2) | 2 | 1 (1) | 2 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Vomiting | 3 | 3 (4) | 0 | 0 | 0 | 0 | 3 | 3 (4) | 2 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Fall | 0 | 0 | 1 | 1 (1) | 1 | 1 (2) | 2 | 2 (3) | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) |
| Flatulence | 1 | 1 (1) | 2 | 1 (1) | 1 | 1 (2) | 4 | 2 (3) | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) |
| Hallucination | 0 | 0 | 3 | 3 (4) | 0 | 0 | 3 | 3 (4) | 0 | 0 | 1 | 1 (3) | 0 | 0 | 1 | 1 (1) |
| Pyrexia | 1 | 1 (1) | 1 | 1 (1) | 0 | 0 | 2 | 2 (3) | 0 | 1 (1) | 0 | 0 | 0 | 0 | 0 | 1 (1) |
| Sleep disorder | 1 | 1 (1) | 1 | 1 (1) | 0 | 0 | 2 | 2 (3) | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) |
| Abdominal discomfort | 1 | 1 (1) | 1 | 1 (1) | 0 | 0 | 2 | 2 (3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain | 0 | 0 | 1 | 1 (1) | 1 | 1 (2) | 2 | 2 (3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Angina pectoris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 (2) | 0 | 0 | 0 | 0 | 2 | 2 (2) |
| Hallucination, visual | 0 | 0 | 4 | 3 (4) | 1 | 1 (2) | 5 | 3 (4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle spasms | 2 | 2 (3) | 0 | 0 | 0 | 0 | 2 | 2 (3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vertigo | 1 | 1 (1) | 2 | 2 (3) | 1 | 1 (2) | 4 | 3 (4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treated during Maintenance | 59 | | 38 | | 58 | | 136 | | 46 | | 60 | | 46 | | 142 | |
| Onset during Maintenance | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Somnolence | 0 | 0 | 7 | 6 (17) | 5 | 4 (8) | 12 | 10 (7) | 2 | 2 (4) | 11 | 7 (12) | 4 | 4 (9) | 17 | 13 (9) |
| Nausea | 3 | 3 (5) | 10 | 5 (14) | 5 | 4 (8) | 18 | 11 (8) | 1 | 1 (2) | 7 | 5 (8) | 8 | 6 (13) | 16 | 12 (8) |
| Depression | 1 | 1 (2) | 0 | 0 | 1 | 1 (2) | 2 | 2 (1) | 1 | 1 (2) | 6 | 0 | 3 | 2 (4) | 4 | 3 (2) |
| Constipation | 0 | 0 | 2 | 1 (3) | 2 | 2 (4) | 4 | 3 (2) | 1 | 1 (2) | 1 | 1 (2) | 2 | 2 (4) | 4 | 4 (3) |
| Dyspepsia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 (2) | 4 | 2 (3) | 1 | 1 (2) | 6 | 4 (3) |
| Headache | 1 | 1 (2) | 1 | 1 (3) | 7 | 1 (2) | 9 | 3 (2) | 0 | 0 | 2 | 2 (3) | 2 | 2 (4) | 4 | 4 (3) |
| Dizziness | 0 | 0 | 3 | 2 (5) | 1 | 1 (2) | 4 | 3 (2) | 2 | 1 (2) | 2 | 2 (3) | 0 | 0 | 4 | 3 (2) |
| Fatigue | 0 | 0 | 1 | 1 (3) | 0 | 0 | 1 | 1 (<1) | 1 | 1 (2) | 1 | 1 (2) | 1 | 1 (2) | 3 | 3 (2) |
| Muscle spasms | 1 | 1 (2) | 1 | 1 (3) | 0 | 0 | 2 | 2 (1) | 1 | 1 (2) | 0 | 0 | 2 | 2 (4) | 3 | 3 (2) |
| Orthostatic hypotension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 3 (5) | 0 | 0 | 4 | 3 (2) |
| Pharyngolaryngeal pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (3) | 1 | 1 (2) | 3 | 3 (2) |
| Vertigo | 1 | 1 (2) | 2 | 1 (3) | 0 | 0 | 3 | 2 (1) | 3 | 2 (4) | 1 | 1 (2) | 0 | 0 | 4 | 3 (2) |
| Back pain | 1 | 1 (2) | 1 | 1 (3) | 1 | 1 (2) | 3 | 3 (2) | 0 | 0 | 2 | 2 (3) | 0 | 0 | 2 | 2 (1) |
| Anxiety | 0 | 0 | 3 | 2 (5) | 1 | 1 (2) | 4 | 3 (2) | 1 | 1 (2) | 0 | 0 | 0 | 0 | 1 | 1 (<1) |
| Edema peripheral | 1 | 1 (2) | 2 | 2 (5) | 0 | 0 | 3 | 3 (2) | 0 | 0 | 2 | 1 (2) | 0 | 0 | 2 | 1 (<1) |
| Insomnia | 0 | 0 | 0 | 0 | 5 | 3 (6) | 5 | 3 (2) | 0 | 0 | 0 | 0 | 1 | 1 (2) | 1 | 1 (<1) |
| Myalgia | 1 | 1 (2) | 2 | 2 (5) | 1 | 1 (2) | 4 | 4 (3) | 0 | 0 | 1 | 1 (2) | 0 | 0 | 1 | 1 (<1) |
| Parkinson's disease | 0 | 0 | 1 | 1 (3) | 2 | 2 (4) | 3 | 3 (2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sleep disorder | 0 | 0 | 0 | 0 | 3 | 3 (6) | 3 | 3 (2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Onset during Titration, Persists into Maintenance | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) | # Events | n (%) |
| Nausea | 2 | 2 (3) | 0 | 0 | 2 | 2 (4) | 4 | 4 (3) | 8 | 8 (9) | 3 | 3 (8) | 0 | 0 | 9 | 9 (11) |
| Somnolence | 2 | 2 (3) | 1 | 1 (2) | 0 | 0 | 3 | 3 (4) | 8 | 8 (10) | 1 | 1 (3) | 0 | 0 | 9 | 8 (10) |
| Dizziness | 1 | 1 (1) | 1 | 1 (2) | 1 | 1 (2) | 3 | 3 (4) | 2 | 2 (3) | 0 | 0 | 0 | 0 | 2 | 2 (3) |
| Headache | 0 | 0 | 0 | 0 | 1 | 1 (2) | 1 | 1 (1) | 2 | 2 (3) | 0 | 0 | 0 | 0 | 2 | 2 (3) |
| Constipation | 3 | 3 (4) | 0 | 0 | 1 | 1 (2) | 4 | 4 (3) | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) |
| Fatigue | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 (3) | 0 | 0 | 0 | 0 | 2 | 2 (3) |
| Flatulence | 0 | 0 | 1 | 1 (3) | 1 | 1 (2) | 2 | 2 (3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lethargy | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) | 2 | 2 (3) | 0 | 0 | 0 | 0 | 2 | 2 (3) |
| Insomnia | 0 | 0 | 0 | 0 | 2 | 2 (4) | 2 | 2 (1) | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) |
| Sleep disorder | 1 | 1 (1) | 1 | 1 (3) | 0 | 0 | 2 | 2 (3) | 1 | 1 (3) | 0 | 0 | 0 | 0 | 1 | 1 (1) |
| Muscle spasms | 2 | 2 (3) | 0 | 0 | 0 | 0 | 2 | 2 (3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hallucination, visual | 0 | 0 | 1 | 1 (3) | 1 | 1 (2) | 2 | 2 (3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 0 | 0 | 0 | 0 | 2 | 2 (4) | 2 | 2 (3) | 0 | 0 | 1 | 1 (3) | 0 | 0 | 1 | 1 (1) |
| Hypertension | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) | 0 | 0 | 2 | 2 (6) | 0 | 0 | 2 | 2 (3) |
| Cough | 1 | 1 (1) | 1 | 1 (3) | 0 | 0 | 2 | 2 (3) | 1 | 1 (1) | 0 | 0 | 0 | 0 | 1 | 1 (1) |
| Erectile dysfunction[2] | 0 | 0/45 | 0 | 0/40 | 0 | 0/30 | 0 | 0/45 | 1 | 1/42 (2) | 0 | 0/27 | 0 | 0 | 1 | 1/42 (2) |

Data Sources: Table 5.72 (# events), Table 5.7 in (%)] (Titration); Table 5.73 (# events), Table 5.8 (n-[%]) (Maintenance Phase); Table 5.74 (# events), Table 5.9 (n [%]) (Persisting into Maintenance); 168 Listing 8.6

Abbreviations: CR=controlled-release; N = total number of subjects; n = number of subjects; TEAE=treatment-emergent adverse event

1. 'Any TEAE' includes both non-gender and gender specific events.
2. These are male-specific AEs so denominator includes only male subjects as noted.

I have constructed a similar table for TEAEs showing an increased risk (based upon treatment difference/effect = ER ropinirole % > placebo %) occurring in study 168 as Table 99 for study 169. Study 168 utilized a 12 week titration period during which 2 treatment sequence groups underwent titration with ER ropinirole and \2 treatment sequence groups underwent titration with IR ropinirole. Patients then were treated over 3 consecutive 8 week maintenance periods during the same treatment used during the titration phase was continued into the first maintenance period. Patients then underwent various formulation switches in the second and third maintenance periods during which they switched to a similar daily dose of the alternative formulation. These incidence of TEAEs during the maintenance phase combines the safety experience in different maintenance periods when using the same formulation.

Table 101 shows TEAEs with an increased risk based upon a treatment difference/effect of at least 2 % for the incidence of TEAEs developing with ER ropinirole treatment vs IR ropinirole treatment. There were few TEAEs (i.e. hallucination, sleep disorder, anxiety) that occurred with a greater frequency during ER ropinirole treatment than with IR ropinirole treatment considering the whole study period. However, during the titration phase, an increased risk with Requip XL compared with immediate-release Requip (shown in descending order of % treatment difference) was observed for: constipation, hallucination, vertigo, abdominal pain/discomfort, nausea, vomiting, fall, headache, diarrhea, pyrexia, and flatulence. During the maintenance phase, an increased risk was observed for fall, myalgia, and sleep disorder. Several adverse reactions developing in the titration phase persisted ($\geq$ 7 days) into the maintenance phase. These "persistent" adverse reactions included: constipation, hallucination, muscle spasms, flatulence, insomnia, sleep disorder, abdominal pain/discomfort cough, and nasopharyngitis.

**Table 101 TEAEs ( ER ropinirole > IR ropinirole By ≥ 2 %) with Onset In Any Phase, In the Titration Phase, In the Maintenance Phase, and Onset in the Titration Phase Persisting into the Maintenance Phase in Study 168 (Early Parkinson's Disease – Monotherapy)**

| TEAE (PT) | Any Study Time | | | Titration Phase | | | Maintenance Phase | | | "Persistent" from Titration Phase into Maintenance Phase | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IR | ER | TE | IR | ER | TE | IR | ER | TE | IR | ER | TE |
| Nausea | | | | 26 | 28 | 2 | | | | | | |
| Headache | | | | 6 | 8 | 2 | | | | | | |
| Diarrhea | | | | 2 | 4 | 2 | | | | | | |
| Vomiting | | | | 2 | 4 | 2 | | | | | | |
| Fall | | | | 1 | 3 | 2 | 0 | 3 | 3 | | | |
| Flatulence | | | | 1 | 3 | 2 | | | | 0 | 3 | 3 |
| Hallucination | 2 | 4 | 2 | 1 | 5 | 4 | | | | 0 | 3 | 3 |
| Abdominal pain/discomfort | | | | 8 | 11 | 3 | | | | 1 | 3 | 2 |
| Pyrexia | | | | 1 | 3 | 2 | | | | | | |
| Muscle spasms | | | | | | | | | | 0 | 3 | 3 |
| Vertigo | | | | 0 | 4 | 4 | | | | | | |
| Constipation | | | | 1 | 6 | 5 | | | | 1 | 6 | 5 |
| Insomnia | | | | | | | | | | 1 | 3 | 2 |
| Sleep disorder | <1 | 4 | >3 | | | | 0 | 2 | 2 | 1 | 3 | 2 |
| Nasopharyngitis | | | | | | | | | | 1 | 3 | 2 |
| Anxiety | 1 | 3 | 2 | | | | | | | | | |
| Myalgia | | | | | | | <1 | 3 | >2 | | | |
| Parkinson's Disease | | | | | | | 0 | 2 | 2 | | | |
| Cough | | | | | | | | | | 1 | 3 | 2 |

Table 102 shows the incidence of "common" TEAEs (≥ 5 %) in study 168 occurring during the titration period and during each maintenance period according to each of the 4 treatment sequences groups (treatment sequence for each of the 3 maintenance periods is shown). In reviewing this table, one should be mindful that the treatment exposure time in each maintenance period (8 weeks) is shorter than the treatment exposure time in the titration period. In general, the frequency of all specific TEAEs appeared to decrease progressively as patients continued treatment throughout the 3 consecutive maintenance periods. **Overall, there was no clear suggestion that switching from the same dose formulation of one formulation to the alternative formulation was associated with an increase in frequency of the most common TEAEs over the second and third maintenance periods.** The only apparent increase in frequency of TEAEs after a formulation switch was an increase in nausea from 3 % in M1 to 19 % in M2 and an increase in somnolence from 0 % in M1 to 4 % in M2 after switching from CR to IR for

the CR-IR-IR sequence group and an increase in headache from 3 % in M1 to 6 % in M2 after switching from CR to IR for the IR-CR-CR sequence group.

**Table 102 Incidence (%) of Subjects With the Most Common TEAEs (≥ 5%) by Study Period, Maintenance Period Treatment Sequence, and Time of First Occurrence (Safety Population: Protocol SK&F-101468/168)**

| | Up-Titration Period (12 Weeks) | Maintenance Period 1 (8 Weeks) | Maintenance Period 2 (8 Weeks) | Maintenance Period 3 (8 Weeks) |
|---|---|---|---|---|
| Sequence | n (%) | n (%) | n (%) | n (%) |
| CR-CR-IR | n=41 | n=39 | n=39 | n=36 |
| All AEs | 24 (59) | 16 (41) | 22 (56) | 10 (28) |
| Nausea | 14 (34) | 3 (8) | 6 (15) | 2 (6) |
| Somnolence | 6 (15) | 4 (10) | 3 (8) | 2 (6) |
| Dizziness | 3 (7) | 1 (3) | 1 (3) | 0 |
| Headache | 5 (12) | 1 (3) | 1 (3) | 0 |
| Constipation | 1 (2) | 1 (3) | 0 | 0 |
| Dyspepsia | 1 (2) | 0 | 0 | 0 |
| Fatigue | 1 (2) | 0 | 0 | 1 (3) |
| CR-IR-IR | n=34 | n=32 | n=27 | n=26 |
| All AEs | 20 (59) | 10 (31) | 11 (41) | 9 (35) |
| Nausea | 7 (21) | 1 (3) | 5 (19) | 1 (4) |
| Somnolence | 2 (6) | 0 | 1 (4) | 0 |
| Dizziness | 3 (9) | 0 | 0 | 0 |
| Headache | 1 (3) | 0 | 1 (4) | 1 (4) |
| Constipation | 3 (9) | 1 (3) | 2 (7) | 0 |
| Dyspepsia | 3 (9) | 0 | 1 (4) | 0 |
| Fatigue | 2 (6) | 1 (3) | 1 (4) | 0 |
| IR-IR-CR | n=43 | n=39 | n=33 | n=30 |
| All AEs | 28 (65) | 13 (33) | 9 (27) | 7 (23) |
| Nausea | 9 (21) | 2 (5) | 1 (3) | 1 (3) |
| Somnolence | 5 (12) | 3 (8) | 3 (9) | 0 |
| Dizziness | 7 (16) | 0 | 1 (3) | 0 |
| Headache | 3 (7) | 1 (3) | 0 | 0 |
| Constipation | 2 (5) | 0 | 1 (3) | 0 |
| Dyspepsia | 3 (7) | 0 | 1 (3) | 0 |
| Fatigue | 3 (7) | 0 | 1 (3) | 0 |
| IR-CR-CR | n=43 | n=40 | n=35 | n=34 |
| All AEs | 27 (63) | 16 (40) | 12 (34) | 11 (32) |
| Nausea | 13 (30) | 3 (8) | 3 (9) | 0 |
| Somnolence | 7 (16) | 4 (10) | 1 (3) | 3 (9) |
| Dizziness | 1 (2) | 2 (5) | 1 (3) | 0 |
| Headache | 2 (5) | 1 (3) | 2 (6) | 0 |
| Constipation | 2 (5) | 1 (3) | 1 (3) | 0 |
| Dyspepsia | 3 (7) | 2 (5) | 0 | 0 |
| Fatigue | 2 (5) | 0 | 0 | 0 |

Data Source: Section 14, Table 8.52, Table 8.53, Table 8.54 and Table 8.55.



## Reviewer Comment

- Many of the observations about the increased frequency of certain TEAEs in the titration period or in the maintenance period or for persisting from the titration into the maintenance period in studies 169 and 168 are worthy of description in the REQUIP XL label.

### 7.1.6 Less Common Adverse Events

- Less common TEAEs (e.g. < 5 % incidence) are shown in the many tables of individual studies or pools of studies in section 7.1.5.3 (Incidence of common adverse events).

### 7.1.7 Laboratory Findings

#### 7.1.7.1 Overview of laboratory testing in the development program

Table 103 outlines the clinical laboratory tests that were performed in each study.

**Table 103 Laboratory Tests Performed in Each Study**

| | Study | | | | |
|---|---|---|---|---|---|
| Parameter | 169[1] | 228[1] | 168[1] | 166[2] | 167[2] |
| **Hematology** | | | | | |
| Hematocrit/ Packed cell volume | ✓ | ✓ | ✓ | ✓ | ✓ |
| Hemoglobin | ✓ | ✓ | ✓ | ✓ | ✓ |
| Platelet count | ✓ | ✓ | ✓ | ✓ | ✓ |
| RBC | ✓ | ✓ | ✓ | ✓ | ✓ |
| WBC | ✓ | ✓ | ✓ | ✓ | ✓ |
| WBC differential | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Clinical Chemistry** | | | | | |
| Alanine aminotransferase (ALT) | ✓ | ✓ | ✓ | ✓ | ✓ |
| Albumin | | | | ✓ | ✓ |
| Globulin | | | | ✓ | ✓ |
| Albumin/Globulin ratio | | | | ✓ | ✓ |
| Alkaline Phosphatase | | | | ✓ | ✓ |
| Aspartate aminotransferase (AST) | ✓ | ✓ | ✓ | ✓ | ✓ |
| Carbon dioxide content/Bicarbonate | ✓ | ✓ | ✓ | | |
| Blood urea nitrogen (BUN)[3] | ✓ | | | | |
| Calcium | ✓ | ✓ | ✓ | ✓ | ✓ |
| Chloride | ✓ | ✓ | ✓ | | |
| Cholesterol (HDL, LDL)[4] | | ✓ | | ✓ | |
| Creatinine | ✓ | ✓ | ✓ | ✓ | ✓ |
| Creatinine phosphokinase | | | | ✓ | |
| Gamma-glutamyl-transferase (GGT) | ✓ | ✓ | ✓ | ✓ | |
| Glucose | ✓ | ✓ | ✓ | ✓ | ✓ |
| Lactate dehydrogenase (LDH) | ✓ | ✓ | ✓ | | |
| Phosphate | | | ✓ | ✓ | ✓ |
| Phosphorus | ✓ | ✓ | | | |
| Potassium | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sodium | ✓ | ✓ | ✓ | ✓ | ✓ |
| Total bilirubin | ✓ | ✓ | ✓ | ✓ | ✓ |
| Total Protein /Serum protein | ✓ | ✓ | ✓ | ✓ | ✓ |
| Triglycerides | | ✓ | | ✓ | |
| Urea | ✓ | ✓ | ✓ | ✓ | ✓ |
| Uric acid | | ✓ | ✓ | | |
| **Urinalysis** | | | | | |
| Blood | ✓ | ✓ | ✓ | ✓ | |
| Glucose | ✓ | ✓ | ✓ | ✓ | |
| Protein | ✓ | ✓ | ✓ | ✓ | |
| If blood or protein noted in urine, microscopy was performed | ✓ | ✓ | ✓ | ✓ | |
| Pregnancy test | ✓ | ✓ | ✓ | ✓ | ✓ |

Source: CSR 169: Section 5.6.3.4 and Section 5.6.3.5; CSR 228: Section: 5.6.3.4; CSR 168: Section 5.6.3.4 and Section 5.6.3.5; CSR 166: Section 5.8.5.2, Table 5; CSR 167: Section 5.6.3.4

1. Laboratory tests were performed by a certified central laboratory.
2. Laboratory tests were performed by a local laboratory.
3. Both BUN and urea were collected in Study 169.
4. Total cholesterol was measured in Study 228 and Study 166. HDL and LDL were measured in Study 228 only.

Table 104 shows the time schedule for various clinical laboratory tests in the individual studies. There were defined windows for collecting laboratory data at specific study visit time points in the individual studies.

**Table 104 Schedule for Laboratory Tests for Individual Studies**

| Study | Study Week | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | S | 1 | 5 | 12 | 24 | 28 | 36 | 104 | FU |
| Pivotal Placebo-Controlled Study (Adjunctive Therapy) [169] | ✓ | | | | ✓* | | | | |
| Controlled Active-Comparator Study (Adjunctive Therapy) [228] | ✓ | | | | | ✓ | | ✓* | ✓ |
| Controlled Active-Comparator Study (Monotherapy) [168] | ✓ | | | ✓** | | | ✓* | | |
| Dosing Regimen – Initial Dose [166] | ✓ | ✓[1] | | | | | | | |
| Dosing Regimen – Optimal Regimen [167] | ✓ | | ✓* | | | | | | |

Source: CSR 169, Section 5.6.3.5, CSR 228, Section 5.6.3.4, CSR 168, Section 5.6.3.5, CSR 166, Section 5.6.3.4 and CSR 167, Section 5.6.3.4
Abbreviations: S, Screening; FU, Follow-up
* Denotes end of treatment/early withdrawal.
** Denotes end of up-titration.
1. Day 8 for Study 166.

**Overview of Data Displays for Laboratory Data**

An overview of the various laboratory data analyses/for individual studies or for a pool of studies 169, 168, and 228 presentations generated for this ISS is provided in Table 105. The "most extreme high" value for a particular parameter for a subject was the highest on-treatment value observed. Similarly, the "most extreme low" value was the lowest value observed. The most extreme high and most extreme low values in the change from screening summaries were calculated by subtracting the screening value from the highest or lowest values for each laboratory parameter for each subject. All subsequent "most extreme high" and "most extreme low" values discussed in this section were derived in the same manner.

In programming the clinical laboratory outputs for the ISS, the first screening assessment for each subject was used. This differs from the approach utilized in the individual studies in which, for subjects with more than one screening assessment, the last screening assessment was used. This difference in approach affected the data for nine subjects (Study 168-3 subjects, Study 169-3 subjects). Of the screening observations not included in the ISS, none were of PCC, and only one (monocytes) was a low value compared with the normal reference range. Thus, the overall conclusions of the laboratory data analysis for the ISS is in agreement with the overall conclusions of the laboratory data analysis for the CSRs.

**Table 105 Overview of Integrated Summary of Safety Data Source Displays for Laboratory Data**

| | All Controlled Phase 3 Studies [169, 228 and 168] | Pivotal Placebo-Controlled Study (Adjunctive Therapy) [169] | Controlled Active-Comparator Study (Adjunctive Therapy) [228] | Controlled Active-Comparator Study (Monotherapy) [168] | Dosing Regimen Study – Initial Dose [166] | Dosing Regimen Study – Optimal Titration [167] |
|---|---|---|---|---|---|---|
| Hematology | | | | | | |
| By-subject listing of hematology values | – | – | CSR 228, Listing 8.5 | – | CSR 166, Listing 38 | IS5 Listing 28 |
| Absolute values | Table 6.39 | Table 6.19 | Table 6.29 | Table 5.1 | – | – |
| Change from Screening | Table 6.40 | Table 6.20 | Table 6.30 | Table 5.2 | | |
| Shifts from Screening | Table 6.43 | Table 6.23 | Table 6.33 | Table 5.9 | Table N07_166 | Table N11_167– |
| Values outside normal reference range | | | | | | |
| During Treatment Period | Table 6.42 | Table 6.22 | Table 6.32 | Table 5.6 | Table N05_166 | Table N10_167 |
| During Titration Period | – | – | – | Table 5.7 | – | – |
| During Maintenance Period | – | – | – | Table 5.8 | – | – |
| POC Values | | | | | | |
| During Treatment Period | Table 6.41 | Table 6.21 | Table 6.31 | Table 5.3 | Table N01_166 | Table N06_167 |
| During Titration Period | – | – | – | Table 5.4 | – | – |
| During Maintenance Period | – | – | – | Table 5.5 | – | – |
| Cell index of subjects with hematology data outside POC range | Cell Index 6.1 | – | – | – | Table N02_166 | Table N07_167 |
| Clinical Chemistry | | | | | | |
| By-subject listing of clinical chemistry values | – | – | CSR 228, Listing 8.5 | – | CSR 166, Listing 39 | IS5 Listing 29 |
| Absolute values | Table 6.44 | Table 6.24 | Table 6.34 | Table 5.10 | – | – |
| Change from Screening | Table 6.45 | Table 6.25 | Table 6.35 | Table 5.11 | | |
| Shifts from Screening | Table 6.48 | Table 6.26 | Table 6.36 | Table 5.18 | Table N07_166 | Table N11_167 |
| Values outside normal reference range | | | | | | |
| During Treatment Period | Table 6.47 | Table 6.27 | Table 6.37 | Table 5.15 | Table N05_166 | Table N10_167 |
| During Titration Period | – | – | – | Table 5.16 | – | – |
| During Maintenance Period | – | – | – | Table 5.17 | – | – |
| POC Values | | | | | | |
| During Treatment Period | Table 6.46 | Table 6.26 | Table 6.36 | Table 5.12 | Table N01_166 | Table N06_167 |
| During Titration Period | – | – | – | Table 5.13 | – | – |
| During Maintenance Period | – | – | – | Table 5.14 | – | – |
| Cell index of subjects with clinical chemistry data outside POC range | Cell Index 6.2 | – | – | – | Table N02_166 | Table N07_167 |
| Laboratory normal ranges and POC values | Appendix A13.1, Section 2 | Appendix A13.1, Section 2 | Appendix A13.1, Section 2 | Appendix A13.1, Section 2 | Appendix A13.1, Section 1 | Appendix A13.1, Section 1 IS5 Listing 26 |

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The main focus was on study 169 but I also looked results other individual studies and the pooled analyses.

7.1.7.3 Standard analyses and explorations of laboratory data

*7.1.7.3.1 Analyses focused on measures of central tendency*

**Reviewer Comment**

- After my review of clinical laboratory analyte analyses for Study 169, there were no clear nor noteworthy mean changes from screening (i.e. essentially the "baseline") to the end of study week 24 for any clinical laboratory analyte (hematology or chemistry) for REQUIP XL.

  Neither did any other analyses of central tendency suggest any concern.

  I did not think that results of these analyses were worthy of presentation.

- The label for rotigotine rotigotine (a recently approved NCE/NME dopaminergic agonist) described some clinical laboratory changes suggesting relatively small effect of rotigotine for decreasing hemoglobin, serum albumin, glucose to hypoglycemic levels in some patients and for increasing BUN. Furthermore, an approvable letter for a controlled-release formulation of ropinirole [redacted] had asked the sponsor to conduct various analyses assessing whether ropinirole produced any similar effects/changes. b(4)

  When I reviewed results for study 169, I paid special attention to these analytes. The mean treatment difference/effect (mean change for ER ropinirole result – mean change for placebo result) for the change from screening/baseline to the end of the study in study 169 was – 0.11 for hemoglobin, -0.13 for hematocrit, -0.01 for total RBCs, 0 for serum creatinine or BUN, and – 0.01 for serum total protein. There was no clear suggestion of any noteworthy effect of ER ropinirole on these specific analytes.

*7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal*

**Reviewer Comment**

- Overall, I did not find that there were any noteworthy/remarkable shifts from normal to abnormal (low or high) for any of the laboratory analytes in study 169 nor in other analyses.

  I did not think that results of these analyses were worthy of presentation.

- As noted above in my comments for analyses of central tendency, I also paid special attention to the shift analyses for the analytes that rotigotine seemed to alter. The mean treatment difference/effect (mean change for ER ropinirole % shift – mean change for placebo % shift) for the change from screening/baseline to the end of the study in study 169 was – 0.8 % for hemoglobin, 0 % for hematocrit, + 0.2 % for total RBCs, 0% for serum creatinine or BUN, and + 1.4 % for serum total protein. There was no suggestion of any noteworthy effect of ER ropinirole on these specific analytes.

*7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities*

Table 106 shows the criteria for outliers of Potential Clinical Concern (PCC).

**Table 106 Outlier Criteria for Clinical Laboratory Values of Potential Clinical Concern (PCC)**

| | F3 Limits | |
|---|---|---|
| | Low | High |
| Haemoglobin (g/dl) | <75% NRL | >115% NRH |
| RBC ($10^{12}$/L) | <80% NRL | >120% NRH |
| WBC ($10^9$/L) | <3 $10^9$/L | >15 $10^9$/L |
| Neutrophils ($10^9$/L or vol %) | <1.5 $10^9$/L or <75% NRL | >150% NRH |
| Lymphocytes (%) | <75% | >150% NRH |
| Monocytes (%) | none | >200% NRH |
| Eosinophils (%) | none | >200% NRH |
| Basophils (%) | none | >200% NRH |
| Platelets ($10^9$/L) | <100 $10^9$/L | >500 $10^9$/L |
| Total Bilirubin (micromoles/L) | none | >150% NRH |
| AST (SGOT) (units) | none | >250% NRH |
| ALT (SGPT) (units) | none | >250% NRH |
| GGT (units) | none | >250% NRH |
| LDH (units) | none | >250% NRH |
| Creatinine (micromoles/L) | <50% NRL | >125% NRH |
| Urea/ BUN (mmol/L) | none | >11 mmol/L |
| Uric Acid (mmol/L) | <50% NRL | >125% NRL |
| Sodium (mmol/L) | <130 mmol/L | >150 mmol/L |
| Potassium (mmol/L) | <3 mmol/L | >5.5 mmol/L |
| Chloride (mmol/L) | <80% NRL | >120% NRH |
| Bicarbonate (mmol/L) | <80% NRL | >120% NRH |
| Glucose (mmol/L) | <2.8 mmol/L | >9.7 mmol/L |
| Calcium (mmol/L) | <1.8 mmol/L | >3.0 mmol/L |
| Phosphate (mmol/L) | <0.5 mmol/L | >1.7 mmol/L |
| Serum Protein (G/L) | <80% NRL | >110% NRH |
| Hematocrit (vol%) | <80%NRL | >120% NRH |

Note: NRL = Normal Range Low and NRH = Normal Range High

**Table 107 Incidence (%) of Subjects With Laboratory Values of Potential Clinical Concern (PCC) at Any On-Treatment Visit (Safety Population: Protocol SK&F-101468/169)**

| Test | PCC Flag[1] | Ropinirole CR N=202 n/N | (%) | Placebo N=191 n/N | (%) |
|---|---|---|---|---|---|
| **Haematology** | | | | | |
| Haematocrit | Low | 0/170 | | 0/161 | |
| | High | 0/170 | | 0/161 | |
| Haemoglobin | Low | 0/170 | | 0/161 | |
| | High | 0/170 | | 0/161 | |
| RBC Count | Low | 1/170 | (<1) | 0/161 | |
| | High | 0/170 | | 0/161 | |
| WBC Count | Low | 1/170 | (<1) | 2/161 | (1) |
| | High | 0/170 | | 0/161 | |
| Basophils | High | 0/170 | | 0/161 | |
| Eosinophils | High | 2/170 | (1) | 0/161 | |
| Lymphocytes | High | 0/170 | | 0/161 | |
| Monocytes | High | 0/170 | | 0/161 | |
| Neutrophils | Low | 1/170 | (<1) | 2/161 | (1) |
| | High | 0/170 | | 0/161 | |
| Platelets | Low | 1/170 | (<1) | 0/160 | |
| | High | 0/170 | | 0/160 | |
| **Liver Function** | | | | | |
| ALT | High | 0/168 | | 0/164 | |
| AST | High | 0/168 | | 0/165 | |
| GGT | High | 0/168 | | 0/165 | |
| LDH | High | 0/168 | | 0/164 | |
| Total Bilirubin | High | 1/168 | (<1) | 0/165 | |
| ALT and Total Bilirubin[2] | High | 0/168 | | 0/164 | |
| **Renal Function and Serum Electrolytes** | | | | | |
| Bicarbonate/ Carbon Dioxide | Low | 0/168 | | 0/165 | |
| | High | 0/168 | | 0/165 | |
| Calcium | Low | 0/168 | | 0/165 | |
| | High | 0/168 | | 0/165 | |
| Chloride | Low | 0/168 | | 0/165 | |
| | High | 0/168 | | 0/165 | |
| Creatinine | Low | 0/168 | | 0/165 | |
| | High | 0/168 | | 3/165 | (2) |
| Potassium | Low | 0/168 | | 0/163 | |
| | High | 1/168 | (<1) | 2/163 | (1) |
| Sodium | Low | 0/168 | | 0/165 | |
| | High | 0/168 | | 0/165 | |
| Urea | High | 0/168 | | 0/165 | |
| **Other** | | | | | |
| Glucose | Low | 0/167 | | 0/165 | |
| | High | 2/167 | (1) | 5/165 | (3) |
| Total Protein | Low | 0/168 | | 0/165 | |
| | High | 0/168 | | 0/165 | |

Data Source: Section 14, Table 8.26 and Table 8.28.
PCC = potential clinical concern.
1. The criteria used for defining values of PCC can be found in the RAP (see Attachment 1).
2. Both ALT and total bilirubin had to be of potential clinical concern for the combination to be flagged as of potential clinical concern.



The proportion of subjects with on-treatment laboratory values that met pre-specified criteria for potential clinical concern was low (≤3% for any parameter) and similar for

both treatment groups. Three of the subjects with on-treatment values that met prespecified
criteria for potential clinical concern had the abnormal value reported as an AE, as follows:

- Subject 5962 (ropinirole CR) had a low RBC count of PCC at Week 24, and an AE report of anemia. This event was not considered to be related to investigational product. There was no change to the dose of investigational product as a result of the AE.
- Subject 5218 (placebo) had a low WBC count of PCC at Week 24, and an AE report of leukopenia. This event was not considered to be related to investigational product. There was no change to the dose of investigational product as a result of the AE.
- Subject 5135 (placebo) had low neutrophil and WBC counts of PCC at Week 24, and an AE report of leukopenia. This event was considered to be related to investigational product. There was no change to the dose of investigational product as a result of the AE.

**Urinalysis**
Urinalysis was conducted at screening and Week 24, or at the subject's withdrawal visit if withdrawn prematurely. At screening a positive urine test was reported for 32/202 subjects (16%) randomized to receive ropinirole CR and 33/189 subjects (17%) randomized to receive placebo. A positive result implied that blood, protein or glucose was present. Of those subjects who had a urine test at Week 24, 31/151 subjects (21%) in the ropinirole CR group and 27/120 subjects (23%) in the placebo group had a positive test result.

**SPONSOR SUMMARY CONCLUSIONS FOR LABORATORY DATA IN CLINICAL STUDIES :**

**Across the clinical development program for ropinirole CR in PD, no clinically relevant changes in laboratory parameters were observed. Specifically, there was no evidence for**
**• mean changes in laboratory parameters**
**• clinically meaningful shifts in laboratory parameters from screening**
**• clinically meaningful changes in laboratory parameters outside the normal reference range**
**• clinically meaningful changes in laboratory abnormalities of PCC**

**Furthermore, no trends or dose effects were noted. Thus, no new clinically important information about the effects of ropinirole on laboratory parameters was observed, and no new safety concerns were identified.**

7.1.7.4 Additional analyses and explorations

- There no additional analyses or exploratory clinical laboratory evaluations other than what has been described above here.

7.1.7.5 Special assessments

- There were no special clinical laboratory assessments.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign measurements were made at:

- all study visits, including screening, for the 3 Controlled Phase 3 studies; and
- screening, hourly for 4 hours post-dose on Day 1 of each week, on Day 4 and at the completion visit for Study 167.

BP and HR were recorded in both the semi-supine and standing positions for the 3 controlled, Phase 3 and 2 dosing-regimen studies. Semi-supine was defined as the subject lying flat with 2 pillows under his/her head. This measurement was taken after the subject had been resting semi-supine for a period of at least 10 minutes. The standing measurements were taken after the subject had been standing for at least 1 minute. One set of vital sign measurements was taken in the semi-supine and standing positions for the 3 controlled studies.

For Study 167, semi-supine BP and HR measurements followed by standing BP and HR measurements were defined as a "set." Three sets of these measurements were recorded to establish a "stable" baseline. Stable was defined as 3 sets of measurements taken within 15 mmHg of the lowest measurement. More than 3 sets of measurements could be made, as long as the last 3 measurements met the requirements for "stable."

Vital signs were to be taken at least 4 hours after study drug dosing for the Pivotal Placebo Controlled Study (Adjunctive Therapy) (Study 169) and the Controlled Active Comparator Study (Monotherapy) (Study 168), and at least 2 hours post-dose for the Controlled Active-Comparator Study (Adjunctive Therapy) (Study 228). If vital signs were taken after a blood draw for PK sampling, the investigator was to ensure that the subject had recovered from the blood draw venipuncture before the BP measurement was taken. The time the measurements were taken was not recorded in the CRF and BP was not assessed immediately prior to dosing for the controlled, Phase 3 studies. Any clinically significant worsening in these assessments was to be recorded on the AE or SAE page of the CRF.

**Reviewer Comment**

- The end of phase 2 meeting minutes noted that study 169 was supposed to collect VS at 4 hours after dosing. However, the protocol noted that VS should be collected **at least 4 hours after dosing (that potentially could be any later time point up to many hours after 4 hours post-dosing).** I \had inquired about this discrepancy from the sponsor and the sponsor noted that it had thought that the

DNP wanted the VS collected at least 4 hours after dosing, It is not clear whether this was a true misunderstanding by the sponsor or whether the final meeting minutes were not written precisely reflecting the DNP position on this issue.

**Eligibility Criteria Relevant to Vital Signs**

Exclusions relevant to vital signs for the 3 controlled, Phase 3 studies were as follows :

- presence or history within the previous 3 months of significant and/or uncontrolled cardiovascular disease (including myocardial infarction, unstable angina pectoris, cardiac arrhythmias, and cerebrovascular accident);
- recent history of severe dizziness or fainting due to postural hypotension on standing.

Exclusions relevant to vital signs for the 2 dosing-regimen studies were as follows:

- a recent history of moderate to severe dizziness, syncope, or orthostatic hypotension (OH) (defined as a fall in BP after rising from semi-supine to standing posture of >30mmHg for SBP or >20mmHg for DBP (Study 167); or
- an erect or supine SBP ≥180mmHg or ≤90mmHg or DBP ≥110mmHg or ≤50mmHg (Study 167)

**Analysis of Vital Sign Measurements**

**Procedures for Assigning Values to Study Visits**

On-treatment vital signs data for the individual study summaries were assigned to visit windows centered around the scheduled time of data collection. Screening, baseline and follow-up visits were not slotted. If a subject had more than 1 assessment within a visit window then the latest assessment was used for summary tables. If a Baseline Visit occurred on the same day as the first dose of Study drug (i.e. Day 1), then it was assumed that the baseline assessments were made prior to treatment. Scheduled collection of VS is shown in Table 108.

Pooled vital signs data for *All Controlled Phase 3 Studies* (Studies 169, 228 and 168) were analyzed at various time points over time. . If a subject had more than 1 assessment within a window the latest assessment was used in the table. The most extreme low and high on-treatment value for each subject was also summarized.

**Table 108 Scheduling for Vital Sign Measurements During the Controlled Phase 3 Studies (Studies 169, 228 and 168) and Dosing Regimen Study – Optimal Titration (Study 167)**

| | | | Study Week | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | S | B | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 40 | 52 | 64 | 76 | 88 | 96 | 104 | FU |
| 169 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓* | | | | | | | | | | | | | | ✓ |
| 228 | ✓ | ✓ | ✓ | | | ✓ | | | ✓ | | | | ✓ | | | | | | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* | ✓ |
| 168 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓* * | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓* | | | | | | | | ✓ |
| 167[1] | ✓ | | ✓ | ✓ | ✓ | ✓ ** | ✓ † | | | | | | | | | | | | | | | | | | | | | | | | |

Source: CSR 169, Table 1; CSR 228, Table 1; CSR 168, Table 1; CSR 167, Attachment 1

* Denotes end of treatment/early withdrawal.

** Denotes end of up-titration.

† Denotes down-titration

Abbreviations: S = screening; B = baseline; FU = follow-up

1. In addition to the weekly clinic visit evaluation, subjects were to have a clinic visit or a home visit mid-week (Day 4 of each week of up-titration) to check for orthostatic BP, HR and AEs. Also, a mid-week telephone call (Day 4 of the week of down-titration) was made to check for AEs.



**Overview of Planned Analyses and Data Presentation**

Vital signs data are presented in this section in the following order: central tendencies (i.e., absolute values and changes from baseline in absolute values over time), outlier analyses, and an overall summary.

Vital signs data in each of these sections are presented by study grouping and individual study in the following order: *All Controlled Phase 3 Studies* (Studies 169, 228 and 168), the Placebo-Controlled Study (Adjunctive Therapy) (Study 169), the Controlled Active-Comparator Study (Adjunctive Therapy) (Study 228), the Controlled Active Comparator Study (Monotherapy) (Study 168), and the *Dosing Regimen Studies* (Initial Dose Selection – [Study 166] and Optimal Titration Regimen – [Study 167]).

An overview of source displays for vital signs data which were generated for this ISS is presented in Table 109. Additional outlier analyses that counted subjects with vital signs meeting outlier criteria according to dose at the time of the event rather than modal dose were also presented.



**Table 109 Overview of Key Source Data Displays for Vital Sign (VS) Data for ISS**

| | All Controlled Phase 3 Studies (Studies 169, 228 and 168) | Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | Controlled Active-Comparator Study (Adjunctive Therapy) (Study 228) | Controlled Active-Comparator Study (Monotherapy) (Study 168) | Dosing Regimen Study – Initial Dose Selection (Study 166) | Dosing Regimen Study – Optimal Titration (Study 167) |
|---|---|---|---|---|---|---|
| Absolute values | Table 7.28 | Table 7.10 | Table 7.19 | Table 7.1 | — | — |
| Change from baseline | Table 7.29 | Table 7.11 | Table 7.20 | Table 7.2 | — | — |
| Incidence of orthostatic hypotension | | | | | | |
| Over time | Table 7.30; Cell Index 7.30 | Table 7.12; Cell Index 7.12 | Table 7.21; Cell Index 7.21 | Table 7.3; Cell Index 7.3 | — | TableN01_167 |
| Threshold change | Table 7.31; Cell Index 7.31 | Table 7.13; Cell Index 7.13 | Table 7.22; Cell Index 7.22 | Table 7.4; Cell Index 7.4 | — | — |
| Threshold change[2] | Table 7.55; Cell Index 7.55 | Table 7.43; Cell Index 7.43 | Table 7.49; Cell Index 7.49 | Table 7.37; Cell Index 7.37 | — | Table N02_167 |
| Vital Signs Meeting Specific Criteria at any On-Treatment Visit | | | | | | |
| Any | Table 7.32; Cell Index 7.32 | Table 7.14; Cell Index 7.14 | Table 7.23; Cell Index 7.23 | Table 7.5; Cell Index 7.5 | Table 24; Cell Index N08_166 | Table N03_167; Cell Index N04_167 |
| Any[2] | Table 7.56; Cell Index 7.56 | Table 7.44; Cell Index 7.44 | Table 7.50; Cell Index 7.50 | Table 7.38; Cell Index 7.38 | | |
| Abnormal vital signs by study period | | | | | | |
| Final Visit | Table 7.33; Cell Index 7.33 | Table 7.15; Cell Index 7.15 | Table 7.24; Cell Index 7.24 | Table 7.6; Cell Index 7.6 | – | – |
| Titration | Table 7.34; Cell Index 7.34 | Table 7.16; Cell Index 7.16 | Table 7.25; Cell Index 7.25 | Table 7.7; Cell Index 7.7 | – | – |
| Maintenance | Table 7.35; Cell Index 7.35 | Table 7.17; Cell Index 7.17 | Table 7.26; Cell Index 7.26 | Table 7.8; Cell Index 7.8 | – | – |
| Persisting | Table 7.36; Cell Index 7.36 | Table 7.18; Cell Index 7.18 | Table 7.27; Cell Index 7.27 | Table 7.9; Cell Index 7.9 | – | – |
| Final Visit[2] | Table 7.57; Cell Index 7.57 | Table 7.45; Cell Index 7.45 | Table 7.51; Cell Index 7.51 | Table 7.39; Cell Index 7.39 | | – |
| Titration[2] | Table 7.58; Cell Index 7.58 | Table 7.46; Cell Index 7.46 | Table 7.52; Cell Index 7.52 | Table 7.40; Cell Index 7.40 | – | – |
| Maintenance[2] | Table 7.59; Cell Index 7.59 | Table 7.47; Cell Index 7.47 | Table 7.53; Cell Index 7.53 | Table 7.41; Cell Index 7.41 | – | – |
| Persisting[2] | Table 7.60; Cell Index 7.60 | Table 7.48; Cell Index 7.48 | Table 7.54; Cell Index 7.54 | Table 7.42; Cell Index 7.42 | – | – |
| Orthostatic drop (standing minus semi-supine) (DBP, SBP) – all subjects | | | | | | |
| Absolute values | — | — | — | — | Table 20, Table 21 | Table 40, Table 41 |
| Change from baseline | — | — | — | — | Table 22, Table 23 | Tables 42, 43 (pre-Wk 1), 44, and 45 (within week) |
| Orthostatic drop (standing minus semi-supine) – subjects with previous dopaminergic therapy[1] | | | | | | |
| Absolute values | — | — | — | — | Table 20a, Table 21a | — |
| Change from baseline | — | — | — | — | Table 22a, Table 23a | — |
| Orthostatic drop (standing minus semi-supine) – subjects without previous dopaminergic therapy[1] | | | | | | |
| Absolute values | — | — | — | — | Table 20b, Table 21b | — |
| Change from baseline | — | — | — | — | Table 22b, Table 23b | — |

Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure; PCC = potential clinical concern

1. Subjects with or without prior dopaminergic therapy included therapy with L-dopa preparations, dopamine agonists, or selegiline.
2. Supplemental outlier analyses that count subjects with events according to the dose at onset of the event or lowest dose at which the event occurred rather than modal dose (as used in the primary analyses).

### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital sign measurements taken during 3 controlled, Phase 3 studies (Studies 169, 228 and 168) and the one dosing regimen study (167) were my main overall focus for VS analyses. Among these studies, I particularly focused on the DNP requested separate

analyses of studies 169, 167, and 168 but most importantly on results of study 169. I also reviewed pooled analyses of studies for the advanced Parkinson's Disease population, all controlled Parkinson's Disease trials, and the pool for studies 169, 228, and 168. Overall, my greatest focus on the various VS analyses was on the DNP outlier criteria for not only the whole study period but also for the titration phase, maintenance phase, and for persistence from the titration phase into the maintenance phase. Although it was not possible to ascertain dose-response data optimally because none of the studies randomized subjects to a fixed dose of ER ropinirole, an attempt was made to assess if there was any suggestion of dose-response in these flexible dose titration studies by also analyzing the data across dose ranges ($\leq$ 8 mg/day, > 8 -16 mg/day, > 16 -24 mg/day, and "any" dose for ER ropinirole).

7.1.8.3 Standard analyses and explorations of vital signs data

*7.1.8.3.1 Analyses focused on measures of central tendencies*

VS data (SBP, DBP, HR, and semi-supine and standing) for Study 169 in the final study report were analyzed for the mean absolute data and the mean data change from baseline over time. For the ISS analyses of study 169, the mean change from baseline was analyzed for the mean highest change and the mean lowest change from baseline. Mean VS changes from baseline were small over time and there were no clear differences between ER ropinirole and placebo.

*7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Some outlier analyses assess the frequency of orthostatic hypotension over time and at any time during the study. Analysis of study 169 showed that there were many instances of increased frequency (vs placebo) of orthostatic hypotension over time throughout the study but not a clearly increased frequency at any specific time.

Table 110 shows the frequency of orthostatic hypotension at any time during the study. The frequency of all these orthostatic hypotension outlier criteria at baseline was similar for ER ropinirole and placebo treatment groups.

**Table 110 Frequency of Orthostatic Hypotension (OH) at Any Time1 by Dose Group for the Ropinirole CR Treatment Group (Page 4 of 4)** ***(Safety Population: Pivotal Placebo-Controlled Study [Adjunctive Therapy][Study 169])***

| | Placebo | | Ropinirole CR | | Ropinirole CR | | Ropinirole CR | | Ropinirole CR | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Dose | | ≤8mg/d | | >8 – 16mg/d | | >16mg/d | | Any Dose | |
| Visit/ OH Parameters Assessed | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) |
| Any On-Treatment Post-Baseline Assessment | | | | | | | | | | |
| SBP OH ≥20mmHg | 59/190 (31) | 59/12 (492) | 50/200 (25) | 50/11 (455) | 37/180 (21) | 37/ 9 (411) | 23/127 (18) | 23/ 9 (256) | 75/200 (38) | 75/11 (682) |
| Severe SBP OH ≥40mmHg | 8/190 (4) | 8/0 (>500) | 5/200 (3) | 5/2 (250) | 4/180 (2) | 4/1 (400) | 1/127 (1) | 1/1 (100) | 9/200 (5) | 9/2 (450) |
| DBP OH ≥10mmHg | 110/190 (58) | 110/30 (367) | 92/200 (46) | 92/34 (271) | 59/180 (33) | 59/30 (197) | 52/127 (41) | 52/25 (208) | 125/200 (63) | 125/34 (368) |
| Severe DBP OH ≥20mmHg | 14/190 (7) | 14/2 (700) | 7/200 (4) | 7/1 (700) | 7/180 (4) | 7/1 (700) | 8/127 (6) | 8/1 (800) | 20/200 (10) | 20/1 (2000) |
| SBP AND DBP OH | 36/190 (19) | 36/5 (720) | 29/200 (15) | 29/ 8 (363) | 19/180 (11) | 19/ 5 (317) | 13/127 (10) | 13/6 (217) | 45/200 (23) | 45/ 8 (563) |
| Severe SBP AND DBP OH | 4/190 (2) | 4/ 0 (>400) | 3/200 (2) | 3/0 (>300) | 3/180 (2) | 3/0 (>300) | 1/127 (1) | 1/ 0 (>100) | 6/200 (3) | 6/0 (>600) |

Data Source: Table 7.12; Listing 8.4, Cell Index 7.12
Abbreviations: CR = controlled-release; SBP = systolic blood pressure; DBP = diastolic blood pressure
1. Observed Relative to Total Number of Subjects Tested and Total Number of Subjects with OH at Baseline
2. Proportion calculated as number of subjects meeting OH criteria at this visit relative to the total number of subjects tested at this visit.
3. Proportion calculated as number of subjects meeting OH criteria at this visit relative to the number of subjects tested at this visit who also met the OH criteria at the baseline assessment.

The most noteworthy (≥ 2 %) treatment difference/effects (ER ropinirole % – Placebo %) for any orthostatic hypotension at any time during the study related to ER ropinirole treatment was 7 % for mild to moderate systolic blood pressure decrements (≥ 20 mm Hg), 5 % for mild to moderate diastolic blood pressure decrements (≥ 10 mm Hg), 3 % for severe diastolic blood pressure decrements (≥ 20 mm Hg), and 4 % for mild to moderate combined systolic and diastolic blood pressure decrements.

To provide additional clinical perspective on these orthostatic VS analyses, an analysis of the randomized, double-blinded, placebo-controlled study in advanced Parkinson's Disease was conducted using a variety of adverse event terms possibly suggestive of hypotension, including hypotension, orthostatic hypotension, dizziness, vertigo, and blood pressure decreased. The incidence of possible hypotension was assessed in each treatment group. This analysis showed a higher incidence of these events with ER ropinirole (7 %) vs placebo (3 %). This increased risk was observed in a setting in which patients were very carefully titrated, and patients with clinically relevant cardiovascular disease or symptomatic orthostatic hypotension at baseline had been excluded from this study. Thus, unselected patients could experience greater abnormalities than the selected patients of study 169.

This increased risk for hypotension (see also additional subsequent outlier analyses) and/or orthostatic hypotension was observed in both the titration and maintenance phases and in some cases persisted into the maintenance period after developing in the titration phase.

Additional VS analyses during treatment were conducted for the incidence of abnormal VS (relative to baseline VS) for supine, and standing positions, and for changing from supine to standing position. These analyses were conducted for occurring at any time

during the study, at the final study visit, in the titration phase, in the maintenance phase, and for persisting from the titration phase into the maintenance phase.

Table 111 shows the incidence of abnormal VS outliers (relative to baseline) **at any visit** for the different positional analyses. There were many VS outliers that showed a noteworthy treatment difference/effect (ER ropinirole % - placebo %) that was ≥ 2 %.

In the semi-supine position, the treatment difference/effect was 2 % for severe systolic blood pressure decrease (≥ 40 mm Hg), 4 % for severe diastolic blood pressure decrease (≥ 20 mm Hg), 3 % for severe systolic blood pressure increase (≥ 40 mm Hg), 5 % for moderate pulse increase (≥ 15 beats/minute), and 2 % for moderate pulse decrease (≥ 15 beats/minute).

In the standing position, the treatment difference/effect was 3 % for severe systolic blood pressure increase (≥ 40 mm Hg), and 5 % moderate pulse decrease (≥ 15 beats/minute).

During the change from supine to standing, the treatment difference/effect was 7 % for moderate systolic blood pressure decrease (≥ 20 mm Hg), 9 % for moderate diastolic blood pressure increase (≥ 10 mm Hg),2 % for severe diastolic blood pressure increase (≥ 20 mm Hg, and 2 % for moderate pulse increase (≥ 15 beats/minute).

These increased risks (based upon treatment differences) for various elevations of systolic and/or diastolic blood pressure and/or changes in pulse was observed in both the titration and maintenance phases and for persisting into the maintenance period after developing in the titration phase.

**Table 111 Incidence of Abnormal Vital Signs at Any Visit During Treatment Relative to Baseline *(Safety Population: Pivotal Placebo-Controlled Study [Adjunctive Therapy] [Study 169])***

| Vital Sign Parameter Category | Treatment Groups by Dose Group (mg/day) for Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | | | | |
|---|---|---|---|---|---|
| | Placebo | Ropinirole CR | | | |
| | Any Dose N=190 n (%) | ≤8 n=24 n (%) | >8 and ≤16 n=60 n (%) | >16 n=116 n (%) | Any Dose N=200 n (%) |
| **Semi-supine** | | | | | |
| SBP increment ≥20mmHg | 66 (35) | 10 (42) | 20 (33) | 28 (24) | 58 (29) |
| SBP increment ≥40mmHg | 10 (5) | 3 (13) | 2 (3) | 10 (9) | 15 (8) |
| SBP decrement ≥20mmHg | 86 (45) | 7 (29) | 22 (37) | 51 (44) | 80 (40) |
| SBP decrement ≥40mmHg | 16 (8) | 0 | 6 (10) | 13 (11) | 19 (10) |
| DBP increment ≥10mmHg | 96 (51) | 9 (38) | 32 (53) | 61 (53) | 102 (51) |
| DBP increment ≥20mmHg | 27 (14) | 5 (21) | 8 (13) | 14 (12) | 27 (14) |
| DBP decrement ≥10mmHg | 122 (64) | 17 (71) | 34 (57) | 73 (63) | 124 (62) |
| DBP decrement ≥20mmHg | 39 (21) | 8 (33) | 13 (22) | 29 (25) | 50 (25) |
| Pulse increment ≥15bpm | 35 (18) | 5 (21) | 11 (18) | 29 (25) | 45 (23) |
| Pulse increment ≥30bpm | 5 (3) | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 33 (17) | 4 (17) | 10 (17) | 24 (21) | 38 (19) |
| Pulse decrement ≥30bpm | 4 (2) | 0 | 1 (2) | 1 (<1) | 2 (1) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 67 (35) | 8 (33) | 24 (40) | 36 (31) | 68 (34) |
| SBP increment ≥40mmHg | 11 (6) | 4 (17) | 4 (7) | 10 (9) | 18 (9) |
| SBP decrement ≥20mmHg | 87 (46) | 9 (38) | 29 (48) | 56 (48) | 94 (47) |
| SBP decrement ≥40mmHg | 20 (11) | 2 (8) | 7 (12) | 15 (13) | 24 (12) |
| DBP increment ≥10mmHg | 101 (53) | 9 (38) | 30 (50) | 67 (58) | 106 (53) |
| DBP increment ≥20mmHg | 30 (16) | 4 (17) | 9 (15) | 19 (16) | 32 (16) |
| DBP decrement ≥10mmHg | 124 (65) | 17 (71) | 38 (63) | 72 (62) | 127 (64) |
| DBP decrement ≥20mmHg | 43 (23) | 7 (29) | 15 (25) | 23 (20) | 45 (23) |
| Pulse increment ≥15bpm | 41 (22) | 6 (25) | 12 (20) | 25 (22) | 43 (22) |
| Pulse increment ≥30bpm | 1 (<1) | 0 | 3 (5) | 1 (<1) | 4 (2) |
| Pulse decrement ≥15bpm | 37 (19) | 6 (25) | 16 (27) | 26 (22) | 48 (24) |
| Pulse decrement ≥30bpm | 3 (2) | 1 (4) | 0 | 1 (<1) | 2 (1) |
| **Change from Semi-supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 37 (19) | 3 (13) | 13 (22) | 22 (19) | 38 (19) |
| SBP increment ≥40mmHg | 3 (2) | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 33 (17) | 6 (25) | 21 (35) | 21 (18) | 48 (24) |
| SBP decrement ≥40mmHg | 4 (2) | 0 | 1 (2) | 2 (2) | 3 (2) |
| DBP increment ≥10mmHg | 78 (41) | 10 (42) | 27 (45) | 62 (53) | 99 (50) |
| DBP increment ≥20mmHg | 17 (9) | 1 (4) | 6 (10) | 14 (12) | 21 (11) |
| DBP decrement ≥10mmHg | 96 (51) | 10 (42) | 30 (50) | 51 (44) | 91 (46) |
| DBP decrement ≥20mmHg | 16 (8) | 2 (8) | 5 (8) | 6 (5) | 13 (7) |
| Pulse increment ≥15bpm | 19 (10) | 2 (8) | 9 (15) | 13 (11) | 24 (12) |
| Pulse increment ≥30bpm | 1 (<1) | 0 | 1 (2) | 0 | 1 (<1) |
| Pulse decrement ≥15bpm | 18 (9) | 3 (13) | 8 (13) | 4 (3) | 15 (8) |
| Pulse decrement ≥30bpm | 3 (2) | 1 (4) | 0 | 0 | 1 (<1) |

Data Source: Table 7.14, Listing 8.4, Cell Index 7.14
Abbreviations: CR = controlled-release; SBP = systolic blood pressure; DBP = diastolic blood pressure



Table 112 shows the incidence of abnormal VS outliers (relative to baseline) **at the final visit** for the different positional analyses.

**Table 112 Incidence of Abnormal Vital Signs at Final Visit During Treatment Relative to Baseline *(Safety Population: Pivotal Placebo- Controlled Study [Adjunctive Therapy] [Study 169])***

| Vital Sign Parameter Category | Treatment Groups by Dose Group (mg/day) for Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | | | | |
|---|---|---|---|---|---|
| | Placebo | Ropinirole CR | | | |
| | Any Dose N=190 | ≤8 n=24 | >8 to ≤16 n=60 | >16 n=116 | Any Dose N=200 |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Semi-supine** | | | | | |
| SBP increment ≥20mmHg | 20 (11) | 5 (21) | 5 (8) | 9 (8) | 19 (10) |
| SBP increment ≥40mmHg | 1 (<1) | 1 (4) | 0 | 1 (<1) | 2 (1) |
| SBP decrement ≥20mmHg | 31 (16) | 2 (8) | 11 (18) | 15 (13) | 28 (14) |
| SBP decrement ≥40mmHg | 4 (2) | 0 | 1 (2) | 6 (5) | 7 (4) |
| DBP increment ≥10mmHg | 34 (18) | 6 (25) | 8 (13) | 18 (16) | 32 (16) |
| DBP increment ≥20mmHg | 1 (<1) | 1 (4) | 2 (3) | 1 (<1) | 4 (2) |
| DBP decrement ≥10mmHg | 49 (26) | 7 (29) | 12 (20) | 28 (24) | 47 (24) |
| DBP decrement ≥20mmHg | 10 (5) | 2 (8) | 3 (5) | 10 (9) | 15 (8) |
| Pulse increment ≥15bpm | 9 (5) | 0 | 1 (2) | 6 (5) | 7 (4) |
| Pulse increment ≥30bpm | 1 (<1) | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 8 (4) | 1 (4) | 3 (5) | 6 (5) | 10 (5) |
| Pulse decrement ≥30bpm | 1 (<1) | 0 | 0 | 0 | 0 |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 28 (15) | 6 (25) | 9 (15) | 9 (8) | 24 (12) |
| SBP increment ≥40mmHg | 2 (1) | 1 (4) | 0 | 3 (3) | 4 (2) |
| SBP decrement ≥20mmHg | 36 (19) | 2 (8) | 13 (22) | 19 (16) | 34 (17) |
| SBP decrement ≥40mmHg | 6 (3) | 0 | 3 (5) | 6 (5) | 9 (5) |
| DBP increment ≥10mmHg | 36 (19) | 5 (21) | 12 (20) | 22 (19) | 39 (20) |
| DBP increment ≥20mmHg | 6 (3) | 1 (4) | 2 (3) | 4 (3) | 7 (4) |
| DBP decrement ≥10mmHg | 56 (29) | 7 (29) | 12 (20) | 26 (22) | 45 (23) |
| DBP decrement ≥20mmHg | 11 (6) | 3 (13) | 4 (7) | 7 (6) | 14 (7) |
| Pulse increment ≥15bpm | 12 (6) | 1 (4) | 1 (2) | 7 (6) | 9 (5) |
| Pulse increment ≥30bpm | 0 | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 11 (6) | 1 (4) | 6 (10) | 10 (9) | 17 (9) |
| Pulse decrement ≥30bpm | 1 (<1) | 1 (4) | 0 | 0 | 1 (<1) |
| **Change from Semi-supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 10 (5) | 1 (4) | 3 (5) | 5 (4) | 9 (5) |
| SBP increment ≥40mmHg | 0 | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 8 (4) | 1 (4) | 3 (5) | 4 (3) | 8 (4) |
| SBP decrement ≥40mmHg | 1 (<1) | 0 | 0 | 0 | 0 |
| DBP increment ≥10mmHg | 30 (16) | 4 (17) | 10 (17) | 22 (19) | 36 (18) |
| DBP increment ≥20mmHg | 2 (1) | 0 | 2 (3) | 4 (3) | 6 (3) |
| DBP decrement ≥10mmHg | 30 (16) | 4 (17) | 7 (12) | 17 (15) | 28 (14) |
| DBP decrement ≥20mmHg | 2 (1) | 1 (4) | 2 (3) | 2 (2) | 5 (3) |
| Pulse increment ≥15bpm | 4 (2) | 0 | 3 (5) | 1 (<1) | 4 (2) |
| Pulse increment ≥30bpm | 0 | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 6 (3) | 1 (4) | 1 (2) | 1 (<1) | 3 (2) |
| Pulse decrement ≥30bpm | 0 | 1 (4) | 0 | 0 | 1 (<1) |

Data Source: Table 7.15, Listing 6.4, Cell Index 7.15
Footnote Slotted by maintenance modal dose or modal dose overall if the subject did not reach maintenance



Table 113 shows the incidence of abnormal VS outliers **during the titration phase** for the different positional analyses.

**Table 113 Incidence of Abnormal Vital Signs <u>During Treatment in the Titration Period</u> *(Safety Population: Pivotal Placebo-Controlled Study [Adjunctive Therapy] [Study 169])***

| Vital Sign Parameter Category | Treatment Groups by Dose Group (mg/day) for Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | | | | |
|---|---|---|---|---|---|
| | Placebo | Ropinirole CR | | | |
| | Any Dose N=190 n (%) | ≤8 n=24 n (%) | >8 to ≤16 n=60 n (%) | >16 n=116 n (%) | Any Dose N=200 n (%) |
| **Semi-supine** | | | | | |
| SBP increment ≥20mmHg | 48 (25) | 5 (21) | 11 (18) | 22 (19) | 38 (19) |
| SBP increment ≥40mmHg | 7 (4) | 2 (8) | 0 | 7 (6) | 9 (5) |
| SBP decrement ≥20mmHg | 70 (37) | 7 (29) | 14 (23) | 42 (36) | 63 (32) |
| SBP decrement ≥40mmHg | 12 (6) | 0 | 2 (3) | 10 (9) | 12 (6) |
| DBP increment ≥10mmHg | 85 (45) | 7 (29) | 19 (32) | 50 (43) | 76 (38) |
| DBP increment ≥20mmHg | 22 (12) | 4 (17) | 3 (5) | 10 (9) | 17 (9) |
| DBP decrement ≥10mmHg | 103 (54) | 13 (54) | 22 (37) | 63 (54) | 98 (49) |
| DBP decrement ≥20mmHg | 29 (15) | 3 (13) | 8 (13) | 21 (18) | 32 (16) |
| Pulse increment ≥15bpm | 25 (13) | 3 (13) | 5 (8) | 17 (15) | 25 (13) |
| Pulse increment ≥30bpm | 4 (2) | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 25 (13) | 2 (8) | 6 (10) | 20 (17) | 28 (14) |
| Pulse decrement ≥30bpm | 2 (1) | 0 | 1 (2) | 1 (<1) | 2 (1) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 52 (27) | 6 (25) | 12 (20) | 27 (23) | 45 (23) |
| SBP increment ≥40mmHg | 8 (4) | 2 (8) | 0 | 6 (5) | 8 (4) |
| SBP decrement ≥20mmHg | 69 (36) | 6 (25) | 17 (28) | 51 (44) | 74 (37) |
| SBP decrement ≥40mmHg | 12 (6) | 1 (4) | 4 (7) | 8 (7) | 13 (7) |
| DBP increment ≥10mmHg | 87 (46) | 8 (33) | 24 (40) | 56 (48) | 88 (44) |
| DBP increment ≥20mmHg | 23 (12) | 3 (13) | 4 (7) | 12 (10) | 19 (10) |
| DBP decrement ≥10mmHg | 104 (55) | 16 (67) | 28 (47) | 61 (53) | 105 (53) |
| DBP decrement ≥20mmHg | 31 (16) | 4 (17) | 9 (15) | 16 (14) | 29 (15) |
| Pulse increment ≥15bpm | 28 (15) | 3 (13) | 10 (17) | 15 (13) | 28 (14) |
| Pulse increment ≥30bpm | 1 (<1) | 0 | 2 (3) | 0 | 2 (1) |
| Pulse decrement ≥15bpm | 27 (14) | 3 (13) | 9 (15) | 18 (16) | 30 (15) |
| Pulse decrement ≥30bpm | 1 (<1) | 1 (4) | 0 | 1 (<1) | 2 (1) |
| **Change from Semi-supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 29 (15) | 1 (4) | 4 (7) | 16 (14) | 21 (11) |
| SBP increment ≥40mmHg | 3 (2) | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 24 (13) | 5 (21) | 11 (18) | 17 (15) | 33 (17) |
| SBP decrement ≥40mmHg | 3 (2) | 0 | 0 | 2 (2) | 2 (1) |
| DBP increment ≥10mmHg | 62 (33) | 7 (29) | 19 (32) | 50 (43) | 76 (38) |
| DBP increment ≥20mmHg | 13 (7) | 0 | 3 (5) | 9 (8) | 12 (6) |
| DBP decrement ≥10mmHg | 70 (37) | 8 (33) | 23 (38) | 41 (35) | 72 (36) |
| DBP decrement ≥20mmHg | 11 (6) | 1 (4) | 3 (5) | 6 (5) | 10 (5) |
| Pulse increment ≥15bpm | 11 (6) | 0 | 7 (12) | 7 (6) | 14 (7) |
| Pulse increment ≥30bpm | 1 (<1) | 0 | 1 (2) | 0 | 1 (<1) |
| Pulse decrement ≥15bpm | 11 (6) | 2 (8) | 5 (8) | 3 (3) | 10 (5) |
| Pulse decrement ≥30bpm | 3 (2) | 1 (4) | 0 | 0 | 1 (<1) |

Data Source: Table 7.16, Listing 6.4, Cell Index 7.16

Table 114 shows the incidence of abnormal VS outliers **<u>during the maintenance phase</u>** for the different positional analyses.

**Table 114 Incidence of Abnormal Vital Signs During Treatment in the Maintenance Period** ***(Safety Population: Pivotal Placebo-Controlled Study [Adjunctive Therapy] [Study 169])***

| Vital Sign Parameter Category | Treatment Groups by Dose Groups (mg/day) for Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | | | | |
|---|---|---|---|---|---|
| | Placebo | Ropinirole CR | | | |
| | Any Dose N=190 n (%) | ≤8 n=24 n (%) | >8 to ≤16 n=60 n (%) | >16 n=116 n (%) | Any Dose N=200 n (%) |
| **Semi-supine** | | | | | |
| SBP increment ≥20mmHg | 40 (21) | 8 (33) | 14 (23) | 19 (16) | 41 (21) |
| SBP increment ≥40mmHg | 7 (4) | 2 (8) | 2 (3) | 6 (5) | 10 (5) |
| SBP decrement ≥20mmHg | 54 (28) | 4 (17) | 19 (32) | 35 (30) | 58 (29) |
| SBP decrement ≥40mmHg | 10 (5) | 0 | 6 (10) | 9 (8) | 15 (8) |
| DBP increment ≥10mmHg | 66 (35) | 8 (33) | 23 (38) | 44 (38) | 75 (38) |
| DBP increment ≥20mmHg | 13 (7) | 3 (13) | 5 (8) | 8 (7) | 16 (8) |
| DBP decrement ≥10mmHg | 77 (41) | 13 (54) | 28 (47) | 55 (47) | 96 (48) |
| DBP decrement ≥20mmHg | 28 (15) | 6 (25) | 11 (18) | 19 (16) | 36 (18) |
| Pulse increment ≥15bpm | 16 (9) | 4 (17) | 9 (15) | 18 (16) | 31 (16) |
| Pulse increment ≥30bpm | 1 (<1) | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 21 (11) | 3 (13) | 10 (17) | 12 (10) | 25 (13) |
| Pulse decrement ≥30bpm | 3 (2) | 0 | 1 (2) | 0 | 1 (<1) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 42 (22) | 6 (25) | 17 (28) | 28 (24) | 51 (26) |
| SBP increment ≥40mmHg | 6 (3) | 4 (17) | 4 (7) | 6 (5) | 14 (7) |
| SBP decrement ≥20mmHg | 54 (28) | 6 (25) | 26 (43) | 38 (33) | 70 (35) |
| SBP decrement ≥40mmHg | 14 (7) | 1 (4) | 6 (10) | 12 (10) | 19 (10) |
| DBP increment ≥10mmHg | 60 (32) | 7 (29) | 21 (35) | 46 (40) | 74 (37) |
| DBP increment ≥20mmHg | 16 (8) | 3 (13) | 5 (8) | 12 (10) | 20 (10) |
| DBP decrement ≥10mmHg | 85 (45) | 13 (54) | 29 (48) | 52 (45) | 94 (47) |
| DBP decrement ≥20mmHg | 28 (15) | 6 (25) | 11 (18) | 18 (16) | 35 (18) |
| Pulse increment ≥15bpm | 24 (13) | 5 (21) | 7 (12) | 17 (15) | 29 (15) |
| Pulse increment ≥30bpm | 0 | 0 | 1 (2) | 1 (<1) | 2 (1) |
| Pulse decrement ≥15bpm | 21 (11) | 5 (21) | 10 (17) | 15 (13) | 30 (15) |
| Pulse decrement ≥30bpm | 3 (2) | 1 (4) | 0 | 0 | 1 (<1) |
| **Change from Semi-supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 17 (9) | 3 (13) | 9 (15) | 15 (13) | 27 (14) |
| SBP increment ≥40mmHg | 0 | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 16 (8) | 5 (21) | 18 (30) | 14 (12) | 37 (19) |
| SBP decrement ≥40mmHg | 3 (2) | 0 | 1 (2) | 0 | 1 (<1) |
| DBP increment ≥10mmHg | 49 (26) | 5 (21) | 21 (35) | 42 (36) | 68 (34) |
| DBP increment ≥20mmHg | 7 (4) | 1 (4) | 3 (5) | 7 (6) | 11 (6) |
| DBP decrement ≥10mmHg | 61 (32) | 8 (33) | 18 (30) | 35 (30) | 61 (31) |
| DBP decrement ≥20mmHg | 8 (4) | 2 (8) | 3 (5) | 3 (3) | 8 (4) |
| Pulse increment ≥15bpm | 15 (8) | 2 (8) | 5 (8) | 9 (8) | 16 (8) |
| Pulse increment ≥30bpm | 0 | 0 | 1 (2) | 0 | 1 (<1) |
| Pulse decrement ≥15bpm | 10 (5) | 2 (8) | 5 (8) | 2 (2) | 9 (5) |
| Pulse decrement ≥30bpm | 0 | 1 (4) | 0 | 0 | 1 (<1) |

Data Source: Table 7.17, Listing 8.4, Cell Index 7.17
Abbreviations: CR = controlled-release; N(n) = total (number) of subjects; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 115 shows the incidence of abnormal VS outliers **persisting from the titration into the maintenance phase** for the different positional analyses.

**Table 115 Incidence of Abnormal Vital Signs Developing During the Titration Period and Persisting into the Maintenance Period *(Safety Population: Pivotal Placebo-Controlled Study [Adjunctive Therapy] [Study 169])***

| Vital Sign Parameter Category | Treatment Groups by Dose Groups (mg/day) for Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | | | | |
|---|---|---|---|---|---|
| | Placebo | Ropinirole CR | | | |
| | Any Dose N=190 n (%) | ≤8 n=24 n (%) | >8 to ≤16 n=60 n (%) | >16 n=116 n (%) | Any Dose N=200 n (%) |
| **Semi-supine** | | | | | |
| SBP increment ≥20mmHg | 22 (12) | 3 (13) | 5 (8) | 13 (11) | 21 (11) |
| SBP increment ≥40mmHg | 4 (2) | 1 (4) | 0 | 3 (3) | 4 (2) |
| SBP decrement ≥20mmHg | 38 (20) | 4 (17) | 11 (18) | 26 (22) | 41 (21) |
| SBP decrement ≥40mmHg | 6 (3) | 0 | 2 (3) | 6 (5) | 8 (4) |
| DBP increment ≥10mmHg | 55 (29) | 6 (25) | 10 (17) | 33 (28) | 49 (25) |
| DBP increment ≥20mmHg | 8 (4) | 2 (8) | 0 | 4 (3) | 6 (3) |
| DBP decrement ≥10mmHg | 58 (31) | 9 (38) | 16 (27) | 45 (39) | 70 (35) |
| DBP decrement ≥20mmHg | 18 (9) | 1 (4) | 6 (10) | 11 (9) | 18 (9) |
| Pulse increment ≥15bpm | 8 (4) | 2 (8) | 3 (5) | 6 (5) | 11 (6) |
| Pulse increment ≥30bpm | 0 | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 13 (7) | 1 (4) | 6 (10) | 8 (7) | 15 (8) |
| Pulse decrement ≥30bpm | 1 (<1) | 0 | 1 (2) | 0 | 1 (<1) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 27 (14) | 4 (17) | 5 (8) | 19 (16) | 28 (14) |
| SBP increment ≥40mmHg | 3 (2) | 2 (8) | 0 | 2 (2) | 4 (2) |
| SBP decrement ≥20mmHg | 36 (19) | 3 (13) | 14 (23) | 33 (28) | 50 (25) |
| SBP decrement ≥40mmHg | 5 (3) | 0 | 3 (5) | 5 (4) | 8 (4) |
| DBP increment ≥10mmHg | 46 (24) | 6 (25) | 15 (25) | 35 (30) | 56 (28) |
| DBP increment ≥20mmHg | 9 (5) | 2 (8) | 0 | 5 (4) | 7 (4) |
| DBP decrement ≥10mmHg | 65 (34) | 12 (50) | 19 (32) | 41 (35) | 72 (36) |
| DBP decrement ≥20mmHg | 15 (8) | 3 (13) | 5 (8) | 11 (9) | 19 (10) |
| Pulse increment ≥15bpm | 11 (6) | 2 (8) | 5 (8) | 7 (6) | 14 (7) |
| Pulse increment ≥30bpm | 0 | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15bpm | 11 (6) | 2 (8) | 3 (5) | 7 (6) | 12 (6) |
| Pulse decrement ≥30bpm | 1 (<1) | 1 (4) | 0 | 0 | 1 (<1) |
| **Change from Semi-supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 9 (5) | 1 (4) | 0 | 9 (8) | 10 (5) |
| SBP increment ≥40mmHg | 0 | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 7 (4) | 4 (17) | 8 (13) | 10 (9) | 22 (11) |
| SBP decrement ≥40mmHg | 2 (1) | 0 | 0 | 0 | 0 |
| DBP increment ≥10mmHg | 33 (17) | 2 (8) | 13 (22) | 30 (26) | 45 (23) |
| DBP increment ≥20mmHg | 3 (2) | 0 | 0 | 2 (2) | 2 (1) |
| DBP decrement ≥10mmHg | 35 (18) | 6 (25) | 11 (18) | 25 (22) | 42 (21) |
| DBP decrement ≥20mmHg | 3 (2) | 1 (4) | 1 (2) | 3 (3) | 5 (3) |
| Pulse increment ≥15bpm | 7 (4) | 0 | 3 (5) | 3 (3) | 6 (3) |
| Pulse increment ≥30bpm | 0 | 0 | 1 (2) | 0 | 1 (<1) |
| Pulse decrement ≥15bpm | 3 (2) | 1 (4) | 2 (3) | 1 (<1) | 4 (2) |
| Pulse decrement ≥30bpm | 0 | 1 (4) | 0 | 0 | 1 (<1) |

Data Source: Table 7.18, Listing 8.4, Cell Index 7.18



## Reviewer Comment

- As shown in the many tables presented here, there were many notable effects of ER ropinirole (vs placebo) for decreasing blood pressure (including orthostatic hypotension) and increasing blood pressure and also increasing and decreasing heart rate. Many of these effects are worthy of description in the label. These results of patients titrated to an optimal treatment dose did not suggest any clear

dose-dependent effects. Similar outlier analyses of abnormal VS in different positions were also conducted for study 168 comparing ER ropinirole to IR ropinirole. Table 116 shows the frequency of orthostatic hypotension for ER ropinirole vs IR ropinirole at any time during treatment in study 168 The most noteworthy (≥ 2 %) treatment difference/ (ER ropinirole % – IR ropinirole %) for any orthostatic hypotension at any time during the study related was 3 % for mild to moderate systolic blood pressure decrements (≥ 20 mm Hg), 4 % for mild to moderate diastolic blood pressure decrements (≥ 10 mm Hg), 4 % for severe diastolic blood pressure decrements (≥ 20 mm Hg), and 3 % for mild to moderate combined systolic and diastolic blood pressure decrements.

**Table 116 Frequency of Orthostatic Hypotension (OH) At Any Time by Dose Group for the Ropinirole CR Treatment Group *(Safety Population: Controlled Active-Comparator Study [Monotherapy] [Study 168])***

| Visit/ OH Parameters Assessed | Ropinirole CR Treatment Group (mg/d) - Study 168 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ≤8mg/d | | >8 - ≤16mg/d | | >16mg/d | | Any Dose (mg/d) | |
| | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) | Proportion[2] n/N (%) | Proportion Relative to Baseline[3] n/N (%) |
| Any On-Treatment Post-Baseline Assessment | | | | | | | | |
| SBP OH ≥20mmHg | 18/122 (15) | 18/ 8 (225) | 13/ 84 (15) | 13/ 3 (433) | 6/54 (11) | 6/2 (300) | 31/140 (22) | 31/6 (383) |
| Severe SBP OH ≥40mmHg | 3/122 (2) | 2/0 (>200) | 1/84 (1) | 1/0 (>100) | 0/54 (0) | 0 | 3/140 (2) | 3/0 (>300) |
| DBP OH ≥10mmHg | 42/122 (34) | 42/12 (350) | 20/84 (24) | 20/ 8 (250) | 19/54 (35) | 19/3 (633) | 62/140 (44) | 62/13 (477) |
| Severe DBP OH ≥20mmHg | 7/122 (6) | 7/0 (>700) | 3/ 84 (4) | 3/0 (>300) | 1/54 (2) | 1/0 (>100) | 10/140 (7) | 10/0 (>1000) |
| SBP AND DBP OH | 11/122 (9) | 11/4 (275) | 7/84 (8) | 7/2 (350) | 3/54 (6) | 3/1 (300) | 19/140 (14) | 19/4 (475) |
| Severe SBP AND DBP OH | 1/122 (1) | 1/0 (>100) | 1/84 (1) | 1/0 (>100) | 0/54 (0) | 0 | 2/140 (1) | 2/0 (>200) |

Additional VS analyses during treatment were conducted for the incidence of abnormal VS (relative to baseline VS) for supine, and standing positions, and for changing from supine to standing position. These analyses were conducted for occurring at any time during the study, at the final study visit, in the titration phase, in the maintenance phase, and for persisting from the titration phase into the maintenance phase.

Table 117 shows the incidence of abnormal VS outliers (relative to baseline) **at any visit** for the different positional analyses.

In the semi-supine position, the treatment difference for ER ropinirole (vs IR ropinirole) was 2 % for moderate systolic blood pressure decrease ((≥ 20 mm Hg), and 4 % for moderate diastolic blood pressure decrease (≥ 10 mm Hg). , severe systolic blood pressure decrease (≥ 40 mm Hg), 4 % for severe diastolic blood pressure decrease (≥ 20 mm Hg), 3 % for severe systolic blood pressure increase (≥ 40 mm Hg), 5 % for moderate pulse increase (≥ 15 beats/minute), and 2 % for moderate pulse decrease (≥ 15 beats/minute).

In the standing position, the treatment difference for ER ropinirole (vs IR ropinirole) was 3 % for moderate systolic blood pressure decrease (≥ 20 mm Hg), 3 % for moderate diastolic blood pressure decrease (≥ 10 mm Hg), and 3 % for severe diastolic blood pressure decrease (≥ 20 mm Hg).

During the change from supine to standing, the treatment difference for ER ropinirole (vs IR ropinirole was 4 % for moderate systolic blood pressure decrease (≥ 20 mm Hg), 3 % for moderate diastolic blood pressure increase (≥ 10 mm Hg), and 4 % for severe diastolic blood pressure increase (≥ 20 mm Hg).

**Table 117 Incidence of Abnormal Vital Signs at Any Visit During Treatment** ***(Safety Population: Controlled Active-Comparator Study [Monotherapy] [Study 168])***

| | Treatment Groups by Dose Group (mg/day) for Controlled Active-Comparator Study (Monotherapy) (Study 168) | | | | |
|---|---|---|---|---|---|
| | Ropinirole IR | Ropinirole CR | | | |
| | Any Dose | ≤8 | >8 and ≤16 | >16 | Any Dose |
| | N=148 | n=53 | n=38 | n=49 | N=140 |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Semi-Supine** | | | | | |
| SBP increment ≥20mmHg | 42 (28) | 12 (23) | 12 (32) | 10 (20) | 34 (24) |
| SBP increment ≥40mmHg | 7 (5) | 1 (2) | 2 (5) | 0 | 3 (2) |
| SBP decrement ≥20mmHg | 64 (43) | 26 (49) | 18 (47) | 19 (39) | 63 (45) |
| SBP decrement ≥40mmHg | 14 (9) | 4 (8) | 4 (11) | 3 (6) | 11 (8) |
| DBP increment ≥10mmHg | 60 (41) | 15 (28) | 15 (39) | 19 (39) | 49 (35) |
| DBP increment ≥20mmHg | 12 (8) | 3 (6) | 5 (13) | 4 (8) | 12 (9) |
| DBP decrement ≥10mmHg | 99 (67) | 30 (57) | 24 (63) | 33 (67) | 87 (62) |
| DBP decrement ≥20mmHg | 32 (22) | 13 (25) | 10 (26) | 14 (29) | 37 (26) |
| Pulse increment ≥15mmHg | 32 (22) | 7 (13) | 11 (29) | 13 (27) | 31 (22) |
| Pulse increment ≥30mmHg | 2 (1) | 0 | 0 | 2 (4) | 2 (1) |
| Pulse decrement ≥15mmHg | 22 (15) | 9 (17) | 6 (16) | 8 (16) | 23 (16) |
| Pulse decrement ≥30mmHg | 4 (3) | 0 | 1 (3) | 1 (2) | 2 (1) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 43 (29) | 10 (19) | 10 (26) | 8 (16) | 28 (20) |
| SBP increment ≥40mmHg | 7 (5) | 2 (4) | 0 | 0 | 2 (1) |
| SBP decrement ≥20mmHg | 59 (40) | 22 (42) | 18 (47) | 20 (41) | 60 (43) |
| SBP decrement ≥40mmHg | 14 (9) | 4 (8) | 4 (11) | 3 (6) | 11 (8) |
| DBP increment ≥10mmHg | 61 (41) | 16 (30) | 13 (34) | 11 (22) | 40 (29) |
| DBP increment ≥20mmHg | 15 (10) | 2 (4) | 5 (13) | 2 (4) | 9 (6) |
| DBP decrement ≥10mmHg | 98 (66) | 32 (60) | 27 (71) | 37 (76) | 96 (69) |
| DBP decrement ≥20mmHg | 37 (25) | 11 (21) | 12 (32) | 16 (33) | 39 (28) |
| Pulse increment ≥15mmHg | 34 (23) | 9 (17) | 11 (29) | 13 (27) | 33 (24) |
| Pulse increment ≥30mmHg | 3 (2) | 2 (4) | 1 (3) | 1 (2) | 4 (3) |
| Pulse decrement ≥15mmHg | 26 (18) | 10 (19) | 3 (8) | 13 (27) | 26 (19) |
| Pulse decrement ≥30mmHg | 1 (<1) | 1 (2) | 0 | 1 (2) | 2 (1) |
| **Change from Semi-Supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 36 (24) | 10 (19) | 7 (18) | 10 (20) | 27 (19) |
| SBP increment ≥40mmHg | 1 (<1) | 1 (2) | 0 | 2 (4) | 3 (2) |
| SBP decrement ≥20mmHg | 22 (15) | 9 (17) | 7 (18) | 10 (20) | 26 (19) |
| SBP decrement ≥40mmHg | 3 (2) | 0 | 1 (3) | 0 | 1 (<1) |
| DBP increment ≥10mmHg | 53 (36) | 18 (34) | 16 (42) | 18 (37) | 52 (37) |
| DBP increment ≥20mmHg | 10 (7) | 4 (8) | 5 (13) | 5 (10) | 14 (10) |
| DBP decrement ≥10mmHg | 64 (43) | 18 (34) | 16 (42) | 28 (57) | 62 (44) |
| DBP decrement ≥20mmHg | 11 (7) | 4 (8) | 3 (8) | 8 (16) | 15 (11) |
| Pulse increment ≥15mmHg | 9 (6) | 3 (6) | 4 (11) | 1 (2) | 8 (6) |
| Pulse increment ≥30mmHg | 1 (<1) | 0 | 1 (3) | 0 | 1 (<1) |
| Pulse decrement ≥15mmHg | 9 (6) | 1 (2) | 2 (5) | 8 (16) | 11 (8) |
| Pulse decrement ≥30mmHg | 1 (<1) | 0 | 0 | 0 | 0 |

Data Source: Table 7.5, Listing 8.1, Cell Index 7.5

These increased risks (based upon treatment differences for ER > IR ropinirole ) for various elevations of systolic and/or diastolic blood pressure and/or changes in pulse was observed in both the titration and maintenance phases and for persisting into the maintenance period after developing in the titration phase. There were many instances in which treatment difference was quite striking (≥ 5 %) for increased risk for ER vs IR ropinirole. These comparisons are shown in Table 118 for the titration period, in Table 119 for the maintenance period, and in Table 120 for TEAEs developing in the titration period and persisting into the maintenance period.

**Table 118** **Incidence of Abnormal Vital Signs During Treatment in the Titration Period** ***(Safety Population: Controlled Active-Comparator Study [Monotherapy] [Study 168])***

| Abnormal Vital Sign Parameters Relative to Baseline/Pre-treatment Vital Signs | n (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Treatment Group | | | | |
| | Ropinirole IR (mg/d) | Ropinirole CR Dose Group (mg/d) | | | |
| | Any Dose N=85 | ≤8 n=8 | >8 and ≤16 n=23 | >16 n=44 | Any Dose N=75 |
| **Semi-Supine** | | | | | |
| SBP increment ≥20mmHg | 25 (29) | 4 (50) | 5 (22) | 10 (23) | 19 (25) |
| SBP increment ≥40mmHg | 5 (6) | 0 | 1 (4) | 0 | 1 (1) |
| SBP decrement ≥20mmHg | 29 (34) | 4 (50) | 11 (48) | 14 (32) | 29 (39) |
| SBP decrement ≥40mmHg | 4 (5) | 0 | 1 (4) | 3 (7) | 4 (5) |
| DBP increment ≥10mmHg | 44 (52) | 0 | 7 (30) | 14 (32) | 21 (28) |
| DBP increment ≥20mmHg | 8 (9) | 0 | 1 (4) | 3 (7) | 4 (5) |
| DBP decrement ≥10mmHg | 50 (59) | 4 (50) | 16 (70) | 29 (66) | 49 (65) |
| DBP decrement ≥20mmHg | 11 (13) | 2 (25) | 4 (17) | 12 (27) | 18 (24) |
| Pulse increment ≥15mmHg | 19 (22) | 2 (25) | 6 (26) | 5 (11) | 13 (17) |
| Pulse increment ≥30mmHg | 2 (2) | 0 | 0 | 2 (5) | 2 (3) |
| Pulse decrement ≥15mmHg | 13 (15) | 3 (38) | 4 (17) | 8 (18) | 15 (20) |
| Pulse decrement ≥30mmHg | 2 (2) | 0 | 1 (4) | 1 (2) | 2 (3) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 26 (31) | 4 (50) | 5 (22) | 8 (18) | 17 (23) |
| SBP increment ≥40mmHg | 4 (5) | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 26 (31) | 4 (50) | 11 (48) | 14 (32) | 29 (39) |
| SBP decrement ≥40mmHg | 3 (4) | 1 (13) | 1 (4) | 3 (7) | 5 (7) |
| DBP increment ≥10mmHg | 45 (53) | 3 (38) | 6 (26) | 9 (20) | 18 (24) |
| DBP increment ≥20mmHg | 11 (13) | 0 | 3 (13) | 1 (2) | 4 (5) |
| DBP decrement ≥10mmHg | 51 (60) | 3 (38) | 16 (70) | 30 (68) | 49 (65) |
| DBP decrement ≥20mmHg | 12 (14) | 1 (13) | 6 (26) | 12 (27) | 19 (25) |
| Pulse increment ≥15mmHg | 18 (21) | 3 (38) | 6 (26) | 11 (25) | 20 (27) |
| Pulse increment ≥30mmHg | 3 (4) | 1 (13) | 1 (4) | 1 (2) | 3 (4) |
| Pulse decrement ≥15mmHg | 17 (20) | 3 (38) | 2 (9) | 11 (25) | 16 (21) |
| Pulse decrement ≥30mmHg | 1 (1) | 1 (13) | 0 | 1 (2) | 2 (3) |
| **Change from Semi-Supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 24 (28) | 1 (13) | 6 (26) | 6 (14) | 13 (17) |
| SBP increment ≥40mmHg | 1 (1) | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 13 (15) | 3 (38) | 3 (13) | 6 (14) | 12 (16) |
| SBP decrement ≥40mmHg | 2 (2) | 0 | 0 | 0 | 0 |
| DBP increment ≥10mmHg | 30 (35) | 3 (38) | 9 (39) | 15 (34) | 27 (35) |
| DBP increment ≥20mmHg | 6 (7) | 2 (25) | 4 (17) | 5 (11) | 11 (15) |
| DBP decrement ≥10mmHg | 36 (42) | 1 (13) | 9 (43) | 19 (43) | 30 (44) |
| DBP decrement ≥20mmHg | 9 (11) | 0 | 2 (9) | 6 (14) | 8 (11) |
| Pulse increment ≥15mmHg | 4 (5) | 1 (13) | 3 (13) | 1 (2) | 5 (7) |
| Pulse increment ≥30mmHg | 0 | 0 | 1 (4) | 0 | 1 (1) |
| Pulse decrement ≥15mmHg | 6 (7) | 0 | 1 (4) | 6 (14) | 7 (9) |
| Pulse decrement ≥30mmHg | 1 (1) | 0 | 0 | 0 | 0 |

Data Source: Table 7.7, Listing 8.1, Cell Index 7.7

**Table 119 Incidence of Abnormal Vital Signs During Treatment in the Maintenance Period** ***(Safety Population: Controlled Active-Comparator Study [Monotherapy] [Study 168])***

| Abnormal Vital Sign Parameters Relative to Baseline/Pre-treatment Vital Signs | n (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Treatment Group | | | | |
| | Ropinirole IR (mg/d) | Ropinirole CR Dose Group (mg/d) | | | |
| | Any Dose N=148 | ≤8 n=53 | >8 and ≤16 n=38 | >16 n=50 | Any Dose N=148 |
| **Semi-Supine** | | | | | |
| SBP increment ≥20mmHg | 27 (18) | 10 (19) | 10 (26) | 2 (4) | 22 (16) |
| SBP increment ≥40mmHg | 4 (3) | 1 (2) | 1 (3) | 0 | 2 (1) |
| SBP decrement ≥20mmHg | 54 (36) | 25 (47) | 16 (42) | 14 (29) | 55 (39) |
| SBP decrement ≥40mmHg | 13 (9) | 4 (8) | 4 (11) | 3 (6) | 11 (8) |
| DBP increment ≥10mmHg | 40 (27) | 15 (28) | 12 (32) | 14 (29) | 41 (29) |
| DBP increment ≥20mmHg | 9 (6) | 3 (6) | 4 (11) | 3 (6) | 10 (7) |
| DBP decrement ≥10mmHg | 82 (55) | 29 (55) | 20 (53) | 26 (53) | 75 (54) |
| DBP decrement ≥20mmHg | 25 (17) | 11 (21) | 9 (24) | 10 (20) | 30 (21) |
| Pulse increment ≥15mmHg | 22 (15) | 6 (11) | 5 (13) | 11 (22) | 22 (16) |
| Pulse increment ≥30mmHg | 0 | 0 | 0 | 1 (2) | 1 (<1) |
| Pulse decrement ≥15mmHg | 14 (9) | 8 (15) | 5 (13) | 4 (8) | 17 (12) |
| Pulse decrement ≥30mmHg | 3 (2) | 0 | 1 (3) | 0 | 1 (<1) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 27 (18) | 9 (17) | 8 (21) | 3 (6) | 20 (14) |
| SBP increment ≥40mmHg | 3 (2) | 2 (4) | 0 | 0 | 2 (1) |
| SBP decrement ≥20mmHg | 51 (34) | 21 (40) | 17 (45) | 14 (29) | 52 (37) |
| SBP decrement ≥40mmHg | 13 (9) | 4 (8) | 4 (11) | 2 (4) | 10 (7) |
| DBP increment ≥10mmHg | 42 (28) | 15 (28) | 10 (26) | 9 (18) | 34 (24) |
| DBP increment ≥20mmHg | 8 (5) | 2 (4) | 4 (11) | 2 (4) | 8 (6) |
| DBP decrement ≥10mmHg | 78 (53) | 30 (57) | 25 (66) | 29 (59) | 84 (60) |
| DBP decrement ≥20mmHg | 31 (21) | 10 (19) | 10 (26) | 9 (18) | 29 (21) |
| Pulse increment ≥15mmHg | 25 (17) | 7 (13) | 7 (18) | 7 (14) | 21 (15) |
| Pulse increment ≥30mmHg | 1 (<1) | 2 (4) | 0 | 1 (2) | 3 (2) |
| Pulse decrement ≥15mmHg | 18 (12) | 9 (17) | 2 (5) | 9 (18) | 20 (14) |
| Pulse decrement ≥30mmHg | 1 (<1) | 0 | 0 | 0 | 0 |
| **Change from Semi-Supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 23 (16) | 9 (17) | 4 (11) | 7 (14) | 20 (14) |
| SBP increment ≥40mmHg | 0 | 1 (2) | 0 | 2 (4) | 3 (2) |
| SBP decrement ≥20mmHg | 12 (8) | 7 (13) | 5 (13) | 6 (12) | 18 (13) |
| SBP decrement ≥40mmHg | 1 (<1) | 0 | 1 (3) | 0 | 1 (<1) |
| DBP increment ≥10mmHg | 40 (27) | 18 (34) | 13 (34) | 11 (22) | 42 (30) |
| DBP increment ≥20mmHg | 7 (5) | 2 (4) | 4 (11) | 2 (4) | 8 (6) |
| DBP decrement ≥10mmHg | 46 (31) | 18 (34) | 12 (32) | 18 (37) | 48 (34) |
| DBP decrement ≥20mmHg | 6 (4) | 4 (8) | 2 (5) | 4 (8) | 10 (7) |
| Pulse increment ≥15mmHg | 6 (4) | 3 (6) | 2 (5) | 0 | 5 (4) |
| Pulse increment ≥30mmHg | 1 (<1) | 0 | 1 (3) | 0 | 1 (<1) |
| Pulse decrement ≥15mmHg | 5 (3) | 1 (2) | 1 (3) | 4 (8) | 6 (4) |
| Pulse decrement ≥30mmHg | 0 | 0 | 0 | 0 | 0 |

Data Source: Table 7.8, Listing 8.1, Cell Index 7.8

**Table 120 Incidence of Abnormal Vital Signs Developing During the Titration Period and Persisting into the Maintenance Period** ***(Safety Population: Controlled Active-Comparator Study [Monotherapy] [Study 168])***

| Abnormal Vital Sign Parameters Relative to Baseline/Pre-treatment Vital Signs | n (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Treatment Group (mg/d) | | | | |
| | Ropinirole IR (mg/d) | Ropinirole CR Dose Group | | | |
| | Any Dose N=85 | ≤8 n=8 | >8 and ≤16 n=23 | >16 n=44 | Any Dose N=75 |
| **Semi-Supine** | | | | | |
| SBP increment ≥20mmHg | 10 (12) | 2 (25) | 3 (13) | 2 (5) | 7 (9) |
| SBP increment ≥40mmHg | 2 (2) | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 19 (22) | 3 (38) | 9 (39) | 9 (20) | 21 (28) |
| SBP decrement ≥40mmHg | 3 (4) | 0 | 1 (4) | 3 (7) | 4 (5) |
| DBP increment ≥10mmHg | 24 (28) | 0 | 4 (17) | 9 (20) | 13 (17) |
| DBP increment ≥20mmHg | 5 (6) | 0 | 0 | 2 (5) | 2 (3) |
| DBP decrement ≥10mmHg | 33 (39) | 3 (38) | 12 (52) | 22 (50) | 37 (49) |
| DBP decrement ≥20mmHg | 4 (5) | 0 | 3 (13) | 8 (18) | 11 (15) |
| Pulse increment ≥15mmHg | 9 (11) | 1 (13) | 0 | 3 (7) | 4 (5) |
| Pulse increment ≥30mmHg | 0 | 0 | 0 | 1 (2) | 1 (1) |
| Pulse decrement ≥15mmHg | 5 (6) | 2 (25) | 3 (13) | 4 (9) | 9 (12) |
| Pulse decrement ≥30mmHg | 1 (1) | 0 | 1 (4) | 0 | 1 (1) |
| **Standing** | | | | | |
| SBP increment ≥20mmHg | 10 (12) | 3 (38) | 3 (13) | 3 (7) | 9 (12) |
| SBP increment ≥40mmHg | 0 | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 18 (21) | 3 (38) | 10 (43) | 8 (18) | 21 (28) |
| SBP decrement ≥40mmHg | 2 (2) | 1 (13) | 1 (4) | 2 (5) | 4 (5) |
| DBP increment ≥10mmHg | 26 (31) | 2 (25) | 3 (13) | 7 (16) | 12 (16) |
| DBP increment ≥20mmHg | 4 (5) | 0 | 2 (9) | 1 (2) | 3 (4) |
| DBP decrement ≥10mmHg | 31 (36) | 1 (13) | 14 (61) | 22 (50) | 37 (49) |
| DBP decrement ≥20mmHg | 6 (7) | 0 | 4 (17) | 5 (11) | 9 (12) |
| Pulse increment ≥15mmHg | 9 (11) | 1 (13) | 2 (9) | 5 (11) | 8 (11) |
| Pulse increment ≥30mmHg | 1 (1) | 1 (13) | 0 | 1 (2) | 2 (3) |
| Pulse decrement ≥15mmHg | 9 (11) | 2 (25) | 1 (4) | 7 (16) | 10 (13) |
| Pulse decrement ≥30mmHg | 1 (1) | 0 | 0 | 0 | 0 |
| **Change from Semi-Supine to Standing** | | | | | |
| SBP increment ≥20mmHg | 11 (13) | 0 | 3 (13) | 3 (7) | 6 (8) |
| SBP increment ≥40mmHg | 0 | 0 | 0 | 0 | 0 |
| SBP decrement ≥20mmHg | 3 (4) | 1 (13) | 1 (4) | 2 (5) | 4 (5) |
| SBP decrement ≥40mmHg | 0 | 0 | 0 | 0 | 0 |
| DBP increment ≥10mmHg | 17 (20) | 3 (38) | 6 (26) | 8 (18) | 17 (23) |
| DBP increment ≥20mmHg | 3 (4) | 0 | 3 (13) | 2 (5) | 5 (7) |
| DBP decrement ≥10mmHg | 18 (21) | 1 (13) | 6 (26) | 9 (20) | 16 (21) |
| DBP decrement ≥20mmHg | 4 (5) | 0 | 1 (4) | 2 (5) | 3 (4) |
| Pulse increment ≥15mmHg | 1 (1) | 1 (13) | 1 (4) | 0 | 2 (3) |
| Pulse increment ≥30mmHg | 0 | 0 | 1 (4) | 0 | 1 (1) |
| Pulse decrement ≥15mmHg | 2 (2) | 0 | 0 | 2 (5) | 2 (3) |
| Pulse decrement ≥30mmHg | 0 | 0 | 0 | 0 | 0 |

Data Source: Table 7.9, Listing 8.1, Cell Index 7.9

*7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities*

The Sponsor conducted analyses of VS outliers based upon values outside the reference range (e.g. Non-potential clinical concern range) : SBP 90-180mmHg, DBP 50-115mmHg, Heart Rate 50-120bpm. Thus, outlier values outside the reference range were SBP > 180 or < 90, DBP > 115 or < 50, and/or HR > 120 or < 50. The sponsor also analyzed values that were arbitrarily designated to be outlier values of Potential Clinical Concern (PCC) including SBP increase or decrease (change) > 30 mm Hg, DBP increase or decrease (change) and > 20 mm Hg. Table 121 shows the sponsors outlier criteria for orthostatic hypotension and other VS threshold changes of interest.

**Table 121 Criteria for Orthostatic Hypotension and Threshold Changes in Vital Signs**

| Parameter | Reference Range | Threshold for Vital Sign Changes |
|---|---|---|
| SBP | 90 to 180mmHg | Increase/Decrease ≥20mmHg |
| | | Increase/Decrease ≥40mmHg |
| | | Increase/Decrease ≥40 to a value of ≤90mmHg |
| DBP | 50 to 115mmHg | Increase/Decrease ≥10mmHg |
| | | Increase/Decrease ≥20mmHg |
| | | Increase/Decrease ≥20 to a value of ≤50mmHg |
| HR | 50 to 120bpm | Increase/Decrease ≥15bpm |
| | | Increase/Decrease ≥30bpm |

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

The incidence (%) of subjects with severe outliers reflecting systolic or diastolic BP values outside the reference range ***and*** with a change from original baseline of potential clinical concern at any on treatment visit is shown in Table 122. Changes from baseline criteria of potential clinical concern were not defined for heart rate.

**Table 122 Severe Low and High BP Change Outliers : Incidence (%) of Subjects With SBP or DBP Outside the Reference Range and With a Change from Baseline of PCC at Any On-Treatment Visit (Safety Population: Protocol SK&F-101468/169)**

| | | | Ropinirole CR N=202 | | Placebo N=191 | |
|---|---|---|---|---|---|---|
| Parameter | Position | Range & Change | n | (%) | n | (%) |
| Systolic BP | Standing | n | 200 | | 190 | |
| | | >180 mmHg & >30 mmHg inc. | 3 | (2) | 0 | |
| | | <90 mmHg & >30 mmHg dec. | 5 | (3) | 2 | (1) |
| | Semi-Supine | n | 200 | | 190 | |
| | | >180 mmHg & >30 mmHg inc. | 3 | (2) | 1 | (<1) |
| | | <90 mmHg & >30 mmHg dec. | 1 | (<1) | 1 | (<1) |
| Diastolic BP | Standing | n | 200 | | 190 | |
| | | >115 mmHg & >20 mmHg inc. | 2 | (1) | 0 | |
| | | <50 mmHg & >20 mmHg dec. | 1 | (<1) | 1 | (<1) |
| | Semi-Supine | n | 200 | | 190 | |
| | | >115 mmHg & >20 mmHg inc. | 4 | (2) | 1 | (<1) |
| | | <50 mmHg & >20 mmHg dec. | 2 | (1) | 1 | (<1) |

Data Source: Section 14, Table 8.5.
inc. = increase; dec. = decrease.

These analyses reflected some quite remarkable/noteworthy severe outliers for BP changes that were increased and decreased. While standing, the treatment difference/effect (ropinirole CR % - placebo %) for the CR formulation was 2 % for severe SBP increment and 1 % for severe DBP increment and was 2 % for severe SBP decrement. While semi-supine, the treatment difference/effect for the CR formulation was 1.5 % for severe SBP increment and 1.5 % for severe DBP increment and was 0.5 % for severe SBP decrement.

**Reviewer Comment**

- ER ropinirole treatment caused an increased risk for severe, combined outliers for blood pressure increment and decrement while semi-supine and standing. The vast majority of these severe outliers occurring during the titration period. These effects should be considered for description in the label.

7.1.8.4 Additional analyses and explorations

The sponsor conducted a study designed to assess the safety of 2 rapid titration schemes for ER ropinirole vs that of a much slower titration scheme for IR ropinirole that is described in its label. Table 123 shows the specific titration schemes for both formulations. Specific attention was paid to assessing orthostatic VS by measuring orthostatic VS at the beginning of each week, at hourly intervals up to 4 hours after dosing, and 4 days after the dose increment.

**Table 123 Dosing Titration Schedules for ER Ropinirole and IR Ropinirole in Study 167**

| Week | Total Ropinirole per Day | | |
|---|---|---|---|
| | Standard IR | CR titration regimen A | CR titration regimen B |
| 1 | 0.75mg | 2mg | 2mg |
| 2 | 1.5mg | 3mg | 4mg |
| 3 | 2.25mg | 4mg | 6mg |
| 4 | 3mg | 6mg | 8mg |
| 5 | 1.5mg | 4mg | 4mg |

Table 124 shows the frequency of orthostatic hypotension at week 4 (before and after initiating the highest dose level) and at week 5 **(at pharmacokinetic steady state for the highest dose level initiated at the beginning of week 4) prior to the daily dose reduction** for each titration scheme and for combined results of both titration schemes for ER ropinirole. In general, the frequency of various orthostatic hypotensive thresholds are more frequent for each ER ropinirole titration group (as well as for the combined results of both ER ropinirole titration groups) compared to results for the IR ropinirole group that had a lower daily dose and a much slower titration rate. The treatment difference % for either ER ropinirole group (vs the IR ropinirole group) for respective outliers is frequently substantial ($\geq$ 5 %) and in some instances ranges as much

as 12-15 %. There does not appear to be a particular time after dosing for which the risk for orthostatic hypotension is clearly increased. Neither does this risk clearly appear to be greater for the slightly more rapid ER ropinirole titration scheme (that also titrated to a higher daily dose) compared to the group titrated to a slightly lower dose and with a slightly slower titration rate.

Table 125 shows the overall frequency of new onset of various orthostatic hypotensive outliers occurring at any time during the study and of moderate and severe pulse changes. Clearly, the risk of orthostatic hypotension for SBP (decrease $\geq$ 20 mm Hg) and DBP (decrease $\geq$ 10 or $\geq$ 20 mm Hg) with ER ropinirole (either titration group) is much greater than the risk for the IR ropinirole group. Although the increased risk for SBP orthostatic hypotension was similar for both ER ropinirole titration group (vs IR), the risk for each DBP outlier was greater for the higher dose and more rapid ER ropinirole titration group.

**Table 124** **Frequency of Orthostatic Hypotension At Weeks 4 and 5** ***(Safety Population: Dosing Regimen Study – Optimal Titration [Study 167])***

| Visit | Orthostatic Hypotension Criteria – Proportion[1] | | | | | |
|---|---|---|---|---|---|---|
| | SBP ≥20mmHg | Severe SBP ≥40mmHg | DBP ≥10mmHg | Severe SBP ≥20mmHg | SBP and DBP | Severe SBP and Severe DBP |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Ropinirole IR, n=22 | | | | | | |
| Week 4, Day 1, Mean Pre-Dose | 1 (5) | 0 | 0 | 0 | 0 | 0 |
| Week 4, Day 1, 1 h Post | 0 | 0 | 0 | 0 | 0 | 0 |
| Week 4, Day 1, 2 h Post | 0 | 0 | 1 (5) | 0 | 0 | 0 |
| Week 4, Day 1, 3 h Post | 0 | 0 | 1 (5) | 0 | 0 | 0 |
| Week 4, Day 1, 4 h Post | 1 (5) | 0 | 1 (5) | 0 | 0 | 0 |
| Week 4, Day 4, Post | 0 | 0 | 0 | 0 | 0 | 0 |
| Week 5, Follow-Up, n=25 | 1 (4) | 0 | 0 | 0 | 0 | 0 |
| Ropinirole CR (Regimen A), n=26 | | | | | | |
| Week 4, Day 1, Mean Pre-Dose | 2 (8) | 0 | 0 | 0 | 0 | 0 |
| Week 4, Day 1, 1 h Post | 4 (15) | 0 | 0 | 0 | 0 | 0 |
| Week 4, Day 1, 2 h Post | 1 (4) | 0 | 1 (4) | 0 | 0 | 0 |
| Week 4, Day 1, 3 h Post | 2 (8) | 0 | 1 (4) | 0 | 1 (4) | 0 |
| Week 4, Day 1, 4 h Post | 1 (4) | 0 | 3 (12) | 0 | 1 (4) | 0 |
| Week 4, Day 4, Post | 0 | 0 | 2 (8) | 1 (4) | 0 | 0 |
| Week 5, Follow-Up, n=25 | 1 (4) | 0 | 3 (12) | 0 | 1 (4) | 0 |
| Ropinirole CR (Regimen B), n=23 | | | | | | |
| Week 4, Day 1, Mean Pre-Dose | 0 | 0 | 0 | 0 | 0 | 0 |
| Week 4, Day 1, 1 h Post | 0 | 0 | 3 (13) | 0 | 0 | 0 |
| Week 4, Day 1, 2 h Post | 0 | 0 | 1 (4) | 0 | 0 | 0 |
| Week 4, Day 1, 3 h Post | 2 (9) | 0 | 2 (9) | 0 | 1 (4) | 0 |
| Week 4, Day 1, 4 h Post | 0 | 0 | 2 (9) | 0 | 0 | 0 |
| Week 4, Day 4, Post | 2 (9) | 0 | 1 (4) | 0 | 1 (4) | 0 |
| Week 5, Follow-Up, n=24 | 2 (8) | 0 | 3 (13) | 0 | 0 | 0 |
| Ropinirole CR (All), n=49 | | | | | | |
| Week 4, Day 1, Mean Pre-Dose | 2 (4) | 0 | 0 | 0 | 0 | 0 |
| Week 4, Day 1, 1 h Post | 4 (8) | 0 | 3 (6) | 0 | 0 | 0 |
| Week 4, Day 1, 2 h Post | 1 (2) | 0 | 2 (4) | 0 | 0 | 0 |
| Week 4, Day 1, 3 h Post | 4 (8) | 0 | 3 (6) | 0 | 2 (4) | 0 |
| Week 4, Day 1, 4 h Post | 1 (2) | 0 | 5 (10) | 0 | 1 (2) | 0 |
| Week 4, Day 4, Post, n=48 | 2 (4) | 0 | 3 (6) | 1 (2) | 1 (2) | 0 |
| Week 5, Follow-Up, n=49 | 3 (6) | 0 | 6 (12) | 0 | 1 (2) | 0 |

Data Sources: Study 167 Table N01_167, Listing 16

1. Proportion calculated as the number of subjects meeting the OH criteria at the dose and visit relative to the number of subjects tested at that dose and visit

Abbreviations: CR = controlled-release; IR = immediate-release; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; OH = Orthostatic Hypotension

Note: IR subjects received a 1mg TID dose during Week 4. CR regimen A (slower) subjects received a 6mg dose and CR regimen B (larger) subjects received an 8mg dose during Week 4. Study completion ended after completion of Week 5.

**Table 125 Incidence of Orthostatic Hypotension (OH)/Vital Sign Threshold Change Observed with a Change from Semi-Supine to Standing Relative to Week 1, Day 1 Pre-Dose at Any Visit *(Safety Population: Dosing Regimen Study – Optimal Titration [Study 167])***

| Orthostatic Vital Sign Threshold | Treatment Groups for Dosing Regimen Study – Optimal Titration (Study 167) | | | |
|---|---|---|---|---|
| | IR | CR Titration Regimen A | CR Titration Regimen B | All CR Doses |
| | N=25 | N=26 | N=24 | N=50 |
| New Onset | | | | |
| SBP decrease ≥20mmHg | 3 (12) | 11 (42) | 8 (33) | 19 (38) |
| SBP decrease ≥40mmHg | 0 | 0 | 0 | 0 |
| SBP decrease ≥40mmHg and value ≤90mmHg | 0 | 0 | 0 | 0 |
| DBP decrease ≥10mmHg | 7 (28) | 10 (39) | 13 (54) | 23 (46) |
| DBP decrease ≥20mmHg | 0 | 2 (8) | 3 (13) | 5 (10) |
| DBP decrease ≥20mmHg and value ≤50mmHg | 0 | 0 | 0 | 0 |
| Pulse increase ≥15bpm | 11 (44) | 12 (46) | 11 (46) | 23 (46) |
| Pulse decrease ≥15bpm | 0 | 1 (4) | 0 | 1 (2) |
| Pulse increase ≥30bpm | 1 (4) | 1 (4) | 0 | 1 (2) |
| Pulse decrease ≥30bpm | 0 | 0 | 0 | 0 |

Table 126 shows the incidence of abnormal VS changes (applying DNP recommended threshold criteria) occurring at any time during treatment while semi-supine, standing, and changing from semi-supine to standing. Overall, the risk for increased outliers was mainly increased for SBP or DBP decrements for both ER ropinirole titration groups. The treatment difference % was frequently substantial (≥ 10 %). In addition, the risk for many of these outliers was frequently greatest for the ER ropinirole group receiving the higher daily dose and faster titration rate. In the semi-supine position, the treatment difference for the most aggressive ER ropinirole (vs IR ropinirole) treatment group was 22 % for moderate SBP decrement (≥ 20 mm Hg), 31 % for moderate DBP decrement (≥ 10 mm Hg), and 17 % for severe DBP decrement (≥ 20 mm Hg). In the standing position, the treatment difference for the most aggressive ER ropinirole (vs IR ropinirole) treatment group was 13 % for severe SBP decrement (≥ 40 mm Hg), 43 % for moderate DBP decrement (≥ 10 mm Hg), and 13 % for severe DBP decrement (≥ 20 mm Hg). While changing from semi-supine to standing, the treatment difference for the most aggressive ER ropinirole (vs IR ropinirole) treatment group was 38 % for moderate SBP increment (≥ 20 mm Hg), and 22 % for moderate DBP decrement (≥ 10 mm Hg).

**Table 126 Incidence of Abnormal Vital Signs Parameters Relative to Week 1, Day 1 Pre-Dose at Any Visit*(Safety Population: Dosing Regimen Study– Optimal Titration [Study 167])***

| | Treatment Groups for Dosing Regimen Study – Optimal Titration (Study 167) | | | |
|---|---|---|---|---|
| | IR | CR Titration Regimen A | CR Titration Regimen B | All CR Doses |
| Parameter | N=25 | N=25 | N=24 | N=50 |
| **Semi-Supine** | | | | |
| SBP increment ≥20mmHg | 7 (28) | 8 (31) | 5 (21) | 13 (26) |
| SBP increment ≥40mmHg | 0 | 0 | 2 (8) | 2 (4) |
| SBP decrement ≥20mmHg | 6 (24) | 10 (29) | 11 (46) | 21 (42) |
| SBP decrement ≥40mmHg | 0 | 2 (8) | 1 (4) | 3 (6) |
| DBP increment ≥10mmHg | 16 (64) | 11 (42) | 11 (46) | 22 (44) |
| DBP increment ≥20mmHg | 1 (4) | 1 (4) | 3 (13) | 4 (8) |
| DBP decrement ≥10mmHg | 9 (36) | 12 (46) | 16 (67) | 28 (56) |
| DBP decrement ≥20mmHg | 1 (4) | 2 (8) | 2 (21) | 7 (14) |
| Pulse increment ≥15mmHg | 5 (20) | 7 (27) | 6 (25) | 13 (26) |
| Pulse increment ≥30mmHg | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15mmHg | 3 (16) | 5 (19) | 1 (4) | 6 (12) |
| Pulse decrement ≥30mmHg | 1 (4) | 0 | 0 | 0 |
| **Standing** | | | | |
| SBP increment ≥20mmHg | 8 (32) | 9 (35) | 7 (29) | 16 (32) |
| SBP increment ≥40mmHg | 2 (8) | 0 | 1 (4) | 1 (2) |
| SBP decrement ≥20mmHg | 6 (24) | 8 (31) | 6 (25) | 14 (28) |
| SBP decrement ≥40mmHg | 0 | 0 | 3 (13) | 3 (6) |
| DBP increment ≥10mmHg | 13 (52) | 13 (50) | 10 (42) | 23 (46) |
| DBP increment ≥20mmHg | 2 (8) | 2 (8) | 2 (8) | 4 (8) |
| DBP decrement ≥10mmHg | 8 (32) | 13 (50) | 18 (75) | 31 (62) |
| DBP decrement ≥20mmHg | 1 (4) | 3 (12) | 4 (17) | 7 (14) |
| Pulse increment ≥15mmHg | 9 (36) | 9 (35) | 5 (21) | 14 (28) |
| Pulse increment ≥30mmHg | 0 | 1 (4) | 0 | 1 (2) |
| Pulse decrement ≥15mmHg | 4 (16) | 4 (15) | 4 (17) | 8 (16) |
| Pulse decrement ≥30mmHg | 1 (4) | 0 | 1 (4) | 1 (2) |
| **Semi-Supine minus Standing** | | | | |
| SBP increment ≥20mmHg | 1 (4) | 6 (23) | 10 (42) | 16 (32) |
| SBP increment ≥40mmHg | 1 (4) | 1 (4) | 1 (4) | 2 (4) |
| SBP decrement ≥20mmHg | 2 (8) | 4 (15) | 4 (17) | 8 (16) |
| SBP decrement ≥40mmHg | 0 | 1 (4) | 0 | 1 (2) |
| DBP increment ≥10mmHg | 12 (48) | 10 (39) | 13 (54) | 23 (46) |
| DBP increment ≥20mmHg | 2 (8) | 1 (4) | 2 (8) | 3 (6) |
| DBP decrement ≥10mmHg | 8 (32) | 9 (35) | 13 (54) | 22 (44) |
| DBP decrement ≥20mmHg | 1 (4) | 1 (4) | 2 (8) | 3 (6) |
| Pulse increment ≥15mmHg | 6 (24) | 2 (8) | 3 (13) | 5 (10) |
| Pulse increment ≥30mmHg | 0 | 0 | 0 | 0 |
| Pulse decrement ≥15mmHg | 4 (16) | 4 (15) | 7 (29) | 11 (22) |
| Pulse decrement ≥30mmHg | 0 | 0 | 0 | 0 |

Data Sources: Table NO3_167; Study 167 Listing 18
Abbreviations: IR = immediate-release; CR = controlled-release; SBP = systolic blood pressure; DBP = diastolic blood pressure
Note: All patients received ≤8mg
Note: New Onset=Not present at baseline but observed during treatment; Not Occurring=Not present at baseline nor observed during treatment
Note: Any visit includes Visit 5, at which time the subjects were off treatment.

**Reviewer Comment**

- These various analyses clearly show that the more aggressive titration scheme for ER ropinirole (both total daily ropinirole dose and titration rate) increases the risk for outlier change responses for blood pressure and heart rate. This increased risk for VS outlier response is particularly applicable to hypotension/orthostatic hypotension. These analyses also show that the more aggressive ER ropinirole titration dosing scheme increases the outlier risk for many outliers including those reflecting hypotensive responses and orthostatic hypotension. **These data argue against the safety of the rapid titration scheme that the sponsor proposes for the label for ER ropinirole.**

**Sponsor Summary of All VS Analyses**

For All Controlled Phase 3 Studies, mean absolute values for vital signs at baseline, at most extreme low and high values on-treatment and at follow-up were within the reference ranges across treatment groups for semi-supine and standing measurements, and orthostatic changes. This finding was consistent for SBP, DBP and HR. The range of minimum and maximum values for orthostatic changes varied widely for the extreme low and high values on-treatment across treatment groups. There were no apparent differences between the placebo and ropinirole CR groups; this comparison is limited due to the issues of combining different studies. In addition, the observed findings are consistent with Parkinson's disease. Similarly, mean changes from baseline in vital signs were small at most extreme low and high values on-treatment and at follow-up. There were no clear treatment-related patterns in changes from baseline to these time points.

There were no apparent differences between placebo and ropinirole CR groups. Any apparent differences between ropinirole CR and the individual control groups may be an artifact of combining studies for the ropinirole CR group, while the control group comes from a single study. There were no consistent dose-related trends seen for change from baseline in absolute vital sign values at most extreme low or high value on-treatment or over time during the All Controlled Phase 3 Studies. There were no consistent dose-related trends seen for mean absolute vital sign values at most extreme low or high value on-treatment or over time during the All Controlled Phase 3 Studies.

The incidences of abnormal vital signs for All Controlled Phase 3 Studies were evaluated by treatment, dose group, body position, and study period (e.g. Titration Phase, Maintenance Phase, and Titration Phase persisting into Maintenance Phase). In general, there were no clear treatment-related or dose-related changes in any outlier group.

Noteworthy observations from individual studies include the following :
• In both Studies 169 and 228, changes from baseline in standing SBP and DBP were noted in the ropinirole CR groups. These changes were generally within 3mmHg of the corresponding measurements in the comparator groups (placebo and Sinemet, respectively) and not clinically significant.

• In Study 228, severe orthostatic decrements in systolic and diastolic blood pressure measurements were low in both ropinirole CR and Sinemet (SBP decrement ≥ 40mmHg: 2% for ropinirole CR versus < 1% for Sinemet; DBP decrement ≥ 20mmHg: 6% for ropinirole CR versus 11% for Sinemet).
• In Study 168, the ropinirole CR and ropinirole IR groups, in general, showed similar patterns of outlier observations except for diastolic change. For any on-treatment measure, an excess of outlier observations for DBP change from baseline ≥ 20mmHg was observed (for semi-supine: 5% for IR and 15% for CR; for standing: 7% for IR and 12% for CR). An excess of outlier observations for the minor diastolic change ≥ 10mmHg was also observed in both postures. These changes were generally small and not clinically significant.
• The incidence of vital sign outliers did not depend on ropinirole CR dose. Within the ropinirole CR group, the greatest number of extreme observations came from the ≤ 8mg dose group. The magnitude of extreme values was similar among the dose groups.
• In each of the phase 3 trials, vital sign outliers were generally more frequent during maintenance than titration, possibly related to the longer duration of the maintenance phase and resultant increased number of vital sign measures.
• In study 166, differences between the ropinirole IR group and the ropinirole CR 2 mg pooled group, which represents the initial dose being recommended for use, were generally of small magnitude and did not follow a consistent pattern.
• In the dosing regimen Study 167, the incidence of vital sign outliers for ropinirole CR regimen B (2,4,6,8mg) was somewhat higher compared to ropinirole IR (0.25mg,0.5mg,0.75mg,1mg TID). The greatest difference was seen in SBP measures and was present in both semi-supine and standing position SBP : for semisupine decrement ≥ 20mmHg (6/25, or 24%, for ropinirole IR versus 11/24, or 46%, for ropinirole CR regimen B) and for the more severe category of SBP decrement ≥ 40mmHg (0/25, or 0% for ropinirole IR versus 1/24, or 4% for ropinirole CR regimen B), as well as for (standing) SBP decrement ≥40mmHg (0/25, or 0% for ropinirole IR versus 3/24 , or 13% for ropinirole CR regimen B). Regimen B subjects titrated to 8mg per day at the end of week 4 whereas the ropinirole IR subjects titrated to 3mg per day in the same time frame.
**In summary, vital sign changes were relatively minor, and unlikely to be of clinical significance.**

## Reviewer Conclusions

- I have noted my more specific comments in various parts of this section.

- I conclude that these various analyses clearly show that ER ropinirole produces many significant changes in VS (both SBP, DBP, and heart rate/pulse) while semi-supine, standing, and changing from supine to standing.

- I disagree with the sponsor's overall conclusion that "vital sign changes were relatively minor and unlikely to be of clinical significance." Some of these VS changes caused by ER ropinirole were relatively quite large in magnitude (e.g. "severe") and in several instances were either much more frequent( or at least notably more frequent) than changes produced by the placebo group or IR

ropinirole group used as the respective comparator, especially in studies 169 and 168, respectively.

- **I think that the changes not only in decreased blood pressure but also in increased blood pressure have the potential to be of clinical significance.** Clinical significance of VS changes produced by ER ropinirole is especially a possibility given the selective design of these studies in which patients with orthostatic hypotension or significant cardiovascular disease or hypertension were generally/typically excluded from study.

- Although the sponsor often noted some treatment differences for ER ropinirole vs a respective comparator (e.g. especially placebo or IR ropinirole), I do not think that the sponsor systematically conducted analyses of these data relative to treatment differences of ER ropinirole to the respective comparator nor appreciated the true potential clinical significance of these treatment differences.

- The VS analyses of study 167 clearly showed the increased risk of VS changes, predominantly hypotensive in nature for the rapid, aggressive titration of ER ropinirole (vs the much slower, more conservative titration for IR ropinirole described in its label).

- Although I agree that the VS analyses that included different ranges of doses did not suggest any dose-dependent effect of ER ropinirole, the design of these studies that did not randomize subjects to fixed ER ropinirole doses but instead typically treated patients with "optimal" flexible doses was not appropriate for assessing dose-dependent effects of ER ropinirole. **I hypothesize that if ER ropinirole was studied in randomized, fixed-dose, parallel group studies, that there would be dose-dependent effects on changes in VS.**

- The various pooled analyses of the 3 pivotal studies and the 2 advanced Parkinson's Disease studies did not suggest any additional, significant information other than the analyses of study 169. Considering the multiple differences in combining results of different studies, I do not think that the pooled analyses provide significant information

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

**Overview of Planned Analyses and Data Presentation**

Results of analyses of ECG data for this section are presented in the following order: the number of subjects with ECGs performed by study visit and dose at time of assessment, global interpretations of ECG findings by the investigator and central cardiology service

b(4)

results of QT correction methods, absolute values and changes from screening in absolute values for each ECG parameter over time, ECG parameter values outside pre-specified reference ranges, ECG parameter values outside the threshold for PCC, maximum increases in QT intervals relative to screening, maximum on-treatment QT interval increases versus dose at time of maximum increase, maximum on-treatment QT interval increases versus HR at time of maximum increase, and a summary of ECG findings. The ECG data are presented by pooled study groupings and individual studies.

An overview of source displays for ECG data which were generated for this ISS is presented in Table 127.

**Table 127 Overview of Key Source Data Displays for Electrocardiogram Data Generated for the Integrated Summary of Safety**

| | All Controlled Phase 3 Studies (Studies 169, 228 and 168) | Pivotal Placebo-Controlled Study (Adjunctive Therapy) (Study 169) | Controlled Active-Comparator Study (Adjunctive Therapy) (Study 228) | Controlled Active-Comparator Study (Monotherapy) (Study 168) | Dosing Regimen Study – Initial Dose Selection (Study 166) | Dosing Regimen Study – Optimal Titration (Study 167) |
|---|---|---|---|---|---|---|
| Absolute values over time | Table 8.19 | Table 8.7 | Table 8.13 | Table 8.1 | Table 25.2, 25.2, 27.2[1] | CSR 167 Table 47, 48, 49 |
| Changes from screening | Table 8.20 | Table 8.8 | Table 8.14 | Table 8.2 | | |
| Values outside reference range | Table 8.21 | Table 8.9 | Table 8.15 | Table 8.3 | Table N05_166 | Table N09_167 |
| PCC values | Table 8.22<br>Cell index 8.1 | Table 8.10 | Table 8.16 | Table 8.4 | Table 166 T101.1<br>Table N09_166<br>Table N10_166 | Table 167 T101.1<br>Table N12_167<br>Table N13_167<br>CSR Listing A4.1 |
| QT >500msec; change >60msec | Table 8.29 | Table 8.11 | Table 8.17 | Table 8.5 | Table N11_166 | Table N14_167 |
| QT outside reference range | Table 8.31 | Table 8.29 | Table 8.30 | Table 8.28 | Table N03_166<br>Table N05_166 | Table N09_167<br>Table N05_167 |
| Maximum on-treatment intervals versus screening value for – | | | | | | |
| – QTcF | Figure 8.28 | Figure 8.10 | Figure 8.19 | Figure 8.1 | — | — |
| – QTcB | Figure 8.29 | Figure 8.11 | Figure 8.20 | Figure 8.2 | — | — |
| – uncorrected QT | Figure 8.30 | Figure 8.12 | Figure 8.21 | Figure 8.3 | — | — |
| – QTc | — | — | — | — | Figure 166 101.1 | Figure 167 101.1 |
| Maximum on-treatment increase from screening versus dose, heart rate or RR interval at maximum increase – | | | | | | |
| – QTcF vs. dose | Figure 8.31 | Figure 8.13 | Figure 8.22 | Figure 8.4 | — | — |
| – QTcB vs. dose | Figure 8.32 | Figure 8.14 | Figure 8.23 | Figure 8.5 | — | — |
| – QT vs. dose | Figure 8.33 | Figure 8.15 | Figure 8.24 | Figure 8.6 | — | — |
| – QTcF vs. heart rate | Figure 8.34 | Figure 8.16 | Figure 8.25 | Figure 8.7 | — | — |
| – QTcB vs. heart rate | Figure 8.35 | Figure 8.17 | Figure 8.26 | Figure 8.8 | — | — |
| – QT vs. heart rate | Figure 8.36 | Figure 8.18 | Figure 8.27 | Figure 8.9 | — | — |
| – QTcF vs. RR interval | Figure 8.46 | Figure 8.42 | Figure 8.45 | Figure 8.39 | — | — |
| – QTcB vs. RR interval | Figure 8.47 | Figure 8.41 | Figure 8.44 | Figure 8.38 | — | — |
| – QT vs. RR interval | Figure 8.46 | Figure 8.40 | Figure 8.43 | Figure 8.37 | — | — |
| Shifts | Table 8.24<br>Table 8.35 | Table 8.12<br>Table 8.33 | Table 8.18<br>Table 8.34 | Table 8.6<br>Table 8.32 | Table N04_166<br>— | CSR Table 90,Table N08_167<br>— |
| QT-change | Table 8.39 | Table 8.37 | Table 8.38 | Table 8.36 | — | — |
| Change to A-NC5 or A-C5 | — | 169 Listing 8.8 | CSR 228 Listing 8.7 | 168 Listing 8.2 | CSR 166 Listing 42 | ISS Listing 31 and CSR A4.1 |
| By-subject listing of ECG values | — | 169 Listing 8.10 | CSR 228 Listing 8.8 | 168 Listing 8.4 | CSR 166 Listing 42, Listing 43 | ISS Listing 31 |

Abbreviations: ECG=electrocardiogram; PCC=potential clinical concern; QTcF=corrected QT baseline (Fridericia); QTcB=corrected QT baseline (Bazett); QTc=corrected QT

1. This is change from Day 1 (pre-dose) for Studies 166 and 167



7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

I have focused on reviewing the ECG results of the individual study 169 that assessed the results of ER ropinirole vs placebo in the only randomized, double-blind, placebo-controlled study in the development program. This study assessed the effect of ER ropinirole in adjunctive treatment of patients with advanced Parkinson's Disease.

**Study 169**

A 12-lead ECG was scheduled at screening and Week 24 (or early withdrawal) for all subjects. Additional 12-lead ECGs were scheduled at baseline, Week 3, Week 8, Week 12, and follow-up by protocol amendment. The majority of the follow-up visits were

obtained while the subjects were on-treatment (88% of the ropinirole CR group and 76% of the placebo group) as this visit generally occurred on the last day of downtitration. ECGs were measured digitally, when possible. **The timing of the ECG assessment was not controlled with regard to time of day, food intake or level of activity.** The ECG tracings were reviewed by the investigator and also sent to a central cardiology service for interpretation. With the exception of the investigator reported ECG data (interpretations reported as normal, abnormal-not clinically significant or abnormal-clinically significant), all ECG presentations are based on the results reported from the central cardiology service ——— interpretation. b(4)

QTcF or QTcB intervals of ≥500 msec and QTcF or QTcB intervals that had increased from screening by > 60 msec were considered to be of particular relevance when investigating whether ropinirole CR had an effect on heart repolarization. Thus, all ECGs from subjects who met these criteria were reviewed by a blinded central ECG reader

——— If a discrepancy was found between ——— interval values and those in the central cardiology service database then ——— was asked to provide a second opinion. Corrections to the clinical trials database were to be made if, upon second review, the central cardiology service reported that an error had been made in the original interpretation of the ECG. b(4)

The central cardiology service ——— provided a second review of all ECGs for subjects, 4859, 5144, 5180 and 5329 as discrepancies were noted between the ECG interval values they calculated and those calculated by ———The central cardiology service identified errors in the screening values for HR, PR, RR, QRS, QT, QTcF and QTcB for subject 5144 only. These errors were corrected prior to database freeze, however, the uncorrected screening values for this subject were erroneously included in data source tables and figures and in the data listing of ECG values. As a result, this subject was erroneously classified as meeting absolute change criteria (>60 msec increase from screening) for QTcF and QTcB at the follow-up visit. The corrected data show that this subject's uncorrected QT, QTcF and QTcB values did not meet criteria for increase relative to screening of >60 msec at any on- treatment visit or at follow-up. The statistical analyses of maximal increase from screening for uncorrected QT, QTcF and QTcB were re-run using the corrected data. b(4)

A screening and at least one on-treatment ECG was obtained for 185 (92%) ropinirole CR subjects and 178 placebo subjects (93%).

7.1.9.3 Standard analyses and explorations of ECG data

*7.1.9.3.1 Analyses focused on measures of central tendency*

**Study 169 ECG Values Over Time**

In general, mean changes from screening in ECG values at on-treatment and follow-up assessments were small for all ECG parameters assessed (heart rate, PR interval, ventricular rate –R-R interval QRS duration, uncorrected QT interval, QTcF interval and QTcB interval) and no differences were apparent between ropinirole CR and placebo. In both ropinirole CR and placebo groups, there was a small decrease in heart rate and increases of PR and RR intervals. Table 128 shows the mean change from screening at different times throughout the study for QTcB and QTcF. The treatment effect (ER ropinirole/CR ropinirole – Placebo) was 4.7 msecs for QTcB and 3.8 msecs for QTcF.

**Table 128 Summary of QTcFridericia (QTcF) and QTcBazett (QTcB) Change From Screening in Study 169**

| | Treatment | N | Visit | n | Mean | SD | Median | Min. | Max. |
|---|---|---|---|---|---|---|---|---|---|
| QTc (Bazett) (msec) | Placebo | 191 | Baseline | 36 | -1.5 | 16.30 | -4.5 | -39 | 45 |
| | | | Week 3 | 44 | -0.3 | 23.37 | -1.0 | -49 | 54 |
| | | | Week 8 | 69 | -0.2 | 24.56 | -1.0 | -49 | 71 |
| | | | Week 12 | 93 | -0.3 | 23.50 | -1.0 | -91 | 51 |
| | | | Week 24 | 123 | -2.1 | 25.79 | -2.0 | -64 | 82 |
| | | | Follow-up | 105 | 1.2 | 22.86 | 2.0 | -66 | 61 |
| | Ropinirole CR | 202 | Baseline | 34 | -3.6 | 22.34 | -4.0 | -59 | 40 |
| | | | Week 3 | 55 | 1.4 | 24.20 | -2.0 | -59 | 51 |
| | | | Week 8 | 80 | 2.7 | 22.15 | -2.0 | -36 | 58 |
| | | | Week 12 | 102 | -0.1 | 24.09 | 3.0 | -56 | 58 |
| | | | Week 24 | 154 | 2.6 | 21.72 | 3.5 | -50 | 59 |
| | | | Follow-up | 113 | -1.2 | 24.93 | -6.0 | -60 | 88 |
| QTc (Fridericia) (msec) | Placebo | 191 | Baseline | 36 | -1.5 | 14.95 | -4.5 | -34 | 44 |
| | | | Week 3 | 44 | -0.3 | 19.17 | 0.5 | -34 | 34 |
| | | | Week 8 | 69 | -0.3 | 21.65 | -1.0 | -61 | 65 |
| | | | Week 12 | 93 | 1.4 | 21.54 | 1.0 | -77 | 46 |
| | | | Week 24 | 123 | -0.3 | 19.85 | -1.0 | -47 | 73 |
| | | | Follow-up | 105 | 2.1 | 20.29 | 3.0 | -55 | 50 |
| | Ropinirole CR | 202 | Baseline | 34 | -2.5 | 19.67 | 0.0 | -48 | 29 |
| | | | Week 3 | 55 | 1.5 | 20.39 | 1.0 | -45 | 62 |
| | | | Week 8 | 80 | 2.6 | 19.34 | 0.0 | -37 | 55 |
| | | | Week 12 | 102 | 1.0 | 20.96 | 1.5 | -42 | 46 |
| | | | Week 24 | 154 | 3.5 | 19.48 | 4.0 | -52 | 61 |
| | | | Follow-up | 113 | -0.8 | 22.55 | -3.0 | -60 | 69 |

Note: The central cardiology service reviewed ECGs where discrepancies were noted between the interval value
they calculated and those calculated by the external cardiologist in his review of ECGs with flagged QT values (>500 msec or >60 msec change from screening). For subject 5144 errors found in HR, PR, RR, QRS,
QT, QTcF and QTcB at screening were corrected prior to database freeze: however, the uncorrected values were
erroneously included in this above table. The corrected data show that this subject's QT, QTcF and QTcB values
did not meet criteria for increase relative to screening >60 msec at any visit including follow-up.

Scatter plots of the maximum on-treatment QTcB or uncorrected QT interval versus the screening interval for each subject, by treatment and dose, were presented. In general for QTcF, QTcB and uncorrected QT, the changes were scattered around the line of equivalency.

Plots of the maximum on-treatment QTcB increase and uncorrected QT increase from screening versus dose at the time of the maximum increase were presented.

Table 129 shows the results of the maximal on treatment QTcB and QTcF change from screening. The adjusted treatment difference for QTcF and QTcB was approximately 2 and 3 msecs, respectively. These differences were not statistically significant as depicted by the p values and 95 % confidence intervals. For QTcF, QTcB and uncorrected QT there was no apparent dose relationship change in either treatment group.

**Table 129 Adjusted Treatment Differences and 95% Confidence Intervals for the Maximal On-Treatment Increases from Screening in QTcF, QTcB and Uncorrected QT (Safety Population: Protocol SK&F-101468/169)**

| Treatment | n | Adjusted Mean Maximal Increase from Screening (SE)[1] | Adjusted Treatment Difference[1] | 95% CI for Treatment Difference[1] | P-value for Treatment Comparison[1] |
|---|---|---|---|---|---|
| **Uncorrected QT** | | | | | |
| Ropinirole CR | 184 | 11.2 (2.53) | 3.7 | (-1.08, 8.43) | 0.1290 |
| Placebo | 177 | 7.5 (2.52) | | | |
| **QTcF** | | | | | |
| Ropinirole CR | 183 | 8.8 (1.97) | 2.4 | (-1.28, 6.14) | 0.1985 |
| Placebo | 177 | 6.3 (1.97) | | | |
| **QTcB** | | | | | |
| Ropinirole CR | 183 | 9.3 (2.26) | 3.1 | (-1.16, 7.35) | 0.1536 |
| Placebo | 177 | 6.2 (2.26) | | | |

Data Source: Section 14, Table 8.24, Table 8.63, Table 8.70.
1. Adjusted for country and value at screening.

The sponsor noted that because these treatment differences for QTcF, QTcB or uncorrected QT interval were < 5 msecs and the upper limits of the 95% confidence interval for the treatment difference were < 10 msecs, the observed differences were not considered to be of clinical relevance.

*7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal*

**Study 169 and Abnormal ECG Parameters**

At screening, 45 subjects (22%) in the ropinirole CR group and 43 subjects (23%) in the placebo group had an abnormal ECG. A similar proportion of subjects had an abnormal ECG at a scheduled on-treatment visit (ropinirole CR: 54 subjects, 29%; placebo: 43 subjects, 24%) or at follow-up (ropinirole CR: 27 subjects, 24%; placebo: 27 subjects, 25%). There were no clear differences in ECG abnormalities according to treatment with ER ropinirole vs placebo.

*7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities*

**Study 169 : Absolute Values Above the Threshold for Potential Clinical Concern (PCC)**

No subject had an absolute on-treatment PR interval, uncorrected QT interval or QRS duration above the threshold for PCC. One subject in each treatment group had a corrected QT interval above the threshold for potential clinical concern (>500 msec). Table 130 summarizes subjects show had a QT/QTc > 60 msecs during treatment compared to screening/baseline.

**Table 130 Summary of Subjects with an Increase in Uncorrected QT, QTcF or QTcB Interval Relative to Screening of More Than 60 msec at Any On-Treatment Visit or Follow-up (Safety Population: Protocol SK&F-101468/169)**

| Interval Data Read by eRT | Ropinirole CR N=202 | | Placebo N=191 | |
|---|---|---|---|---|
| Inc. | n/N | (%) | n/N | (%) |
| **Increase of >60 msec from Screening at any On-Treatment Visit** | | | | |
| QT [subjects] | 6/184 [4673, 4857, 5147, 5210, 5971, 6075] | (3) | 3/177 [4899, 5010, 5176] | (2) |
| QTcF [subjects] | 2/183 [4673, 5329[1]] | (1) | 2/177 [4859, 5027] | (1) |
| QTcB [subjects] | 1/183 [5329[1]] | (<1) | 4/177 [4701, 4859, 4865, 5027] | (2) |

Data Source: Section 14, Table 8.21, Table 8.22, Table 8.60, Table 8.61, Table 8.67, Table 8.68.

1. Subject 5329 had an increases in QTcF and QTcB of >60 msec from screening. As this subject's on-treatment visit (at the time of early withdrawal) was outside the scheduled on-treatment visit windows for ECG (Week 3, 8, 12 or 24), this subject's data has not been included in the summary tabulations in Section 14. However, for completeness, this subject has been included in this in-text table.



7.1.9.4 Additional analyses and explorations

**Sponsor Summary of ECG Data Analyses**

The sponsor noted that substantial ECG monitoring was conducted during the clinical development of ropinirole CR with 2191 ECGs obtained for 674 PD subjects receiving ropinirole CR. The study population was representative of subjects who would be eligible for clinical trials in PD; i.e., many of these subjects were elderly with possible background ECG abnormalities and were taking concomitant medications which might also have been a confounder. These evaluations included appropriate external review.

Changes from screening in absolute values were small and variable with no consistent or dose-related trends including ECGs performed at the maximum dose grouping of > 20mg/day. Regarding the potential effect on cardiac repolarization, the data were analyzed according to current standards with multiple analysis for each parameter. QTcF was shown to be a better correction relative to QTcB.

There was no apparent effect on cardiac repolarization per PCC values for any of the dose groups evaluated including > 20mg/day.

The incidence of treatment-emerging abnormalities of QT/QTc intervals was low, with no dose-dependence, and no differences between treatment groups. The mean change from screening in most extreme QTcF interval showed a between-group difference of under 2.0msec for the placebo and ropinirole CR groups in Study 169 and a difference of 3.0msec for the ropinirole CR and Sinemet groups in Study 228 (in both cases, the interval with ropinirole CR was longer than that for the comparator). These differences are well within generally accepted safety limits.

There was no dose-related effect, or time-of-treatment effect of ropinirole CR on any ECG parameter.

QTcF did not show unexpected dependence on baseline QTcF, or on HR at time of maximal change. The dataset did not show a clinically relevant liability of ropinirole on cardiac repolarization as assessed by the effect on QT/QTc interval.

**Reviewer Conclusions**

- I do not conclude that there was any clearly increased risk of ECG abnormalities associated with ER ropinirole treatment (vs Placebo).

7.1.10 Immunogenicity

- Not applicable

7.1.11 Human Carcinogenicity

- There were no new concerns raised with respect to human carcinogenicity for this new formulation (ER ropinirole) of this approved drug immediate-release ropinirole.

- Not applicable

7.1.12 Special Safety Studies

Potential for QT or QTc prolongation : The sponsor had conducted and submitted previously a special study evaluating the potential for QTc prolongation with ropinirole treatment. The exposure-response re-analysis was previously reviewed by Interdisciplinary Review Team for QT Studies (QT-IRT) [redacted] for RLS. The overall review findings indicate that there was no clear QTc prolongation with therapeutic doses of ropinirole. However, the effect of higher exposures achieved either due to drug interactions, hepatic failure, or at higher doses has not been systematically evaluated. b(4)

- Not applicable

7.1.13 Withdrawal Phenomena and/or Abuse Potential

- There were no new concerns raised with respect to this subject for this new formulation (ER ropinirole) of this approved drug immediate-release ropinirole.

7.1.14 Human Reproduction and Pregnancy Data

- There were no new concerns raised with respect to this subject for this new formulation (ER ropinirole) of this approved drug immediate-release ropinirole.

7.1.15 Assessment of Effect on Growth

- Not applicable

7.1.16 Overdose Experience

- There were no new concerns raised with respect to this subject for this new formulation (ER ropinirole) of this approved drug immediate-release ropinirole

7.1.17 Postmarketing Experience

SPONSOR SUMMARY OF POST-MARKETING EXPERIENCE WITH IR ROPINIROLE

Because ropinirole CR is not yet approved in any country, there is no post marketing experience with this formulation. However, post-marketing experience with ropinirole IR is extensive, with an estimated cumulative exposure of approximately 350,696,000 patient days (960,811 patient years) as of March 2006.

As of 31 May 2006, GSK has received a total of 3506 spontaneous reports of adverse events in subjects receiving ropinirole IR. As expected, the vast majority of reports involve Parkinson's disease patients. Of these reports, 55 involved a fatal outcome. AEs leading to a fatal outcome were diverse in nature. In four cases, the reporters considered the AEs leading to death as possibly or probably related to ropinirole IR treatment (suspected cardiac arrhythmia, vasculitis which progressed to gangrene, unknown cause of death in a patient with coronary artery disease, and pneumonia, bilateral pleural effusion, mediastinal and hilar lymphadenopathy, and features suggestive of basal fibrosis of an indeterminate cause.

Nine hundred twenty six reports met the FDA definition of a serious adverse event. The body system distribution for these serious events were broadly similar to nonserious events, with the most common body systems including nervous system disorders (414), psychiatric disorders (326), general disorders and administration site conditions (216), gastrointestinal disorders (124) and injury poisoning and procedural complications (100). The reviews of safety data have continued to show that ropinirole IR is a well-tolerated drug in the treatment of Parkinson's disease /RLS. The information included in the current USPI reflects the post-marketing experience with ropinirole to date.

The total cumulative exposure of ropinirole IR from market experience up to March 2006 is approximately 350,696,000 patient days (960,811 patient years). The sponsor noted that the reviews of safety data have continued to show that ropinirole is a well-tolerated drug in the treatment of Parkinson's disease/RLS.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

The bulk of the patient exposure was derived from controlled studies 169, 168, and 228 and open-label extensions for patients with early and advanced Parkinson's Disease.

#### 7.2.1.2 Demographics

All age groups were well represented in the safety population for All PD patient studies, with approximately half of subjects ≥65 years old (387/746; 52%), as would be expected for subjects with PD. Nearly one-third (107/387; 28%) of this elderly population was 75 years of age or older. The majority of PD subjects aged 18-64 years old and ≥65 years old received ropinirole CR at modal doses > 8mg/day (217/359 [60%], and 237/387 [61%], respectively). One-hundred thirty-four (134) subjects aged 18-64 years old (37%) and 146/387 (38%) of subjects ≥65 years old received ropinirole CR for >52 weeks. A slightly lower proportion of the subset of elderly subjects aged ≥75 years (31/107; 29%) were exposed to ropinirole CR for >52 weeks. Of those subjects in each age category who received ropinirole CR for >52 weeks, 113/134 (84%) subjects aged 18-64 had modal doses >8mg/day, while 114/146 (78%) of those subjects ≥65 years old had a modal dose >8mg/day.

For any exposure to ropinirole CR, more males (449/746; 60%) than females (297/746; 40%) were enrolled in the All PD studies. Males and females were evenly distributed within each duration of exposure strata (≤26 weeks, >26 weeks and ≤52 weeks, and >52 weeks), with approximately one-third of both males and females in each category. The majority of males (285/449; 63%) and females (169/297; 57%) were exposed to ropinirole CR modal doses >8mg/day.
One-hundred seventy (170) males (38%) and 110 females (37%) were exposed to ropinirole CR for > 52 weeks. The majority of males (145/170; 85%) and females (82/110; 75%) exposed for >52 weeks had a modal doses >8mg/day.

**Reviewer Comment**

- There were no concerns with regard to the adequacy of dose-duration exposures based upon gender or age (especially relative to "elderly patients).

#### 7.2.1.3 Extent of exposure (dose/duration)

**All PD Studies**

Ropinirole CR data were pooled for analysis across All PD studies. Table 131 summarizes exposure to ropinirole CR by modal dose for all PD studies.

**Table 131 Summary of Exposure to Ropinirole CR by Modal Dose1*(Safety Population: All PD Studies)***

| Duration of Exposure (Weeks) | All PD Studies (Studies 168/169/228/164/165/166/167/196/248) N = 746 | | | |
|---|---|---|---|---|
| | ≤8mg/d n (%)[2] | >8 – 16mg/d n (%)[2] | >16mg/d n (%)[2] | Any Dose N (%)[2] |
| ≤26 weeks | 162 (55) | 42 (18) | 33 (15) | 237 (32) |
| >26 weeks, and ≤52 weeks | 77 (26) | 82 (35) | 70 (32) | 229 (31) |
| >52 weeks | 53 (18) | 110 (47) | 117 (53) | 280 (38) |
| Any Exposure, n/N (%) | 292/746 (39) | 234/746 (31) | 220/746 (29) | 746 (100) |

Data Source: Table 3.1, d=day
Cut-off date: January 24, 2006

1. Subjects were assigned according to their overall duration of exposure to ropinirole CR and according to overall modal dose. Modal dose for a subject was defined as the most commonly used dose during the parent and extension studies. Subjects were enumerated in only 1 cell of the matrix in this mutually exclusive display.
2. Percentages were based on the number of subjects in the modal dose group rather than the number of subjects in the treatment group.



Subjects were assigned according to their overall duration of exposure to ropinirole CR and according to overall modal dose. Modal dose for a subject was defined as the most commonly used dose during the parent and extension studies. Subjects were enumerated in only 1 cell of the matrix in this mutually exclusive display.

Percentages were based on the number of subjects in the modal dose group rather than the number of subjects in the treatment group. Across all clinical studies in PD subjects, a total of 746 subjects were exposed to ropinirole CR. A total of 509 subjects (68%) received ropinirole CR for at least 6 months and 280 subjects received ropinirole CR for more than a year.

More than one-third of all exposed subjects received ropinirole CR for > 52 weeks (280/746; 38%), and of these, 81% (227/280) had a modal dose > 8mg/day. At the higher modal dose (> 16mg/day), a larger proportion of subjects (117/220; 53%) were exposed to ropinirole CR for > 52 weeks.

Thirty-nine percent (39%) of all PD subjects had a modal dose ≤ 8mg/day, 31% had a modal dose between 8 and 16mg/day, and 29% had a modal doses > 16mg/day. Of the 39% of subjects who had a modal dose ≤ 8mg/day, 55% (162/292 subjects) received ropinirole CR for < 6 months, reflecting the inclusion of the short-duration, low-dose clinical pharmacology studies in PD subjects (Studies 164 and 165), as well as the dosing regimen studies (Studies 166 and 167).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

- Not applicable

7.2.2.2 Postmarketing experience

Because ropinirole CR is not yet approved in any country, there is no post marketing experience with this formulation. However, post-marketing experience with ropinirole IR is extensive, with an estimated cumulative exposure of approximately 350,696,000 patient days (960,811 patient years) as of March 2006.

As of 31 May 2006, GSK has received a total of 3506 spontaneous reports of adverse events in subjects receiving ropinirole IR. As expected, the vast majority of reports involve Parkinson's disease patients. Of these reports, 55 involved a fatal outcome. AEs leading to a fatal outcome were diverse in nature. In four cases, the reporters considered the AEs leading to death as possibly or probably related to ropinirole IR treatment (suspected cardiac arrhythmia, vasculitis which progressed to gangrene, unknown cause of death in a patient with coronary artery disease, and pneumonia, bilateral pleural effusion, mediastinal and hilar lymphadenopathy, and features suggestive of basal fibrosis of an indeterminate cause.

Nine hundred twenty six reports met the FDA definition of a serious adverse event. The body system distribution for these serious events were broadly similar to nonserious events, with the most common body systems including nervous system disorders (414), psychiatric disorders (326), general disorders and administration site conditions (216), gastrointestinal disorders (124) and injury poisoning and procedural complications (100). The sponsor noted that the reviews of safety data have continued to show that ropinirole IR is a well-tolerated drug in the treatment of Parkinson's disease /RLS.

**Reviewer Comment**

- The post-marketing review did not suggest any new or clear safety signals.

7.2.2.3 Literature

**Reviewer Comment**

- Although the sponsor provided a list of references, the sponsor did not provide a review or discussion of the published literature.

7.2.3 Adequacy of Overall Clinical Experience

**Reviewer Comment**

- I considered the overall clinical experience studied and presented to be adequate for assessing the safety and efficacy of ER ropinirole.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

- Not applicable

7.2.5 Adequacy of Routine Clinical Testing

**Reviewer Comment**

- I considered the routine clinical testing to be adequate for assessing the safety and efficacy of ER ropinirole.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

**Reviewer Comment**

- I considered the metabolic, clearance, and interaction workup to be adequate as did the Clinical Pharmacology review

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

**Reviewer Comment**

- I considered this NDA evaluation to be adequate for assessing safety of this new formulation for its potential approval.

7.2.8 Assessment of Quality and Completeness of Data

**Reviewer Comment**

- I considered the quality and completeness of data to be adequate for assessing the safety and efficacy of ER ropinirole.

7.2.9 Additional Submissions, Including Safety Update

**Sponsor Summary Of Contents of 120-Day Safety Update**

This 120-Day Safety Update summarizes additional safety information for REQUIP® (ropinirole hydrochloride; SK&F-101468) XL 24-Hour™ Extended Release Tablets for Parkinson's disease (PD), hereafter referred to as ropinirole controlled release (CR) tablets. This update summarizes safety information from 3 ongoing studies available since the cut-off date for the safety information in New Drug Application (NDA) 22-008, which was submitted to the Food and Drug Administration (FDA) on 9 February 2007. The data cut-off dates for this safety update are 16 November 2006 for data in the clinical trials database and 31 January 2007 for data (deaths, serious adverse events (SAEs) and pregnancies) in the Operating Companies Event Accession and Notification System (OCEANS) safety database.

Studies 196 and 248 are ongoing multicenter, long-term, open-label, flexible dose extension studies of ropinirole CR (2 to 24mg/day) for the treatment of subjects with PD. When relevant, safety data from Studies 196 and 248, have been integrated to give an '*Open-Label Extension Studies*' population.

Study 105323 is an ongoing, multicenter, randomized, double-blind, double-dummy, parallel group study designed to demonstrate the superiority of 24 weeks of therapy using ropinirole CR (2 to 24mg/day) compared to the currently marketed ropinirole immediate release (IR) tablets (0.25 to 8mg three times daily) in subjects with advanced stage Parkinson's Disease who are not optimally controlled on levodopa (L-dopa).

When relevant, data from completed studies in subjects with PD have been integrated with data from ongoing Studies 196 and 248, to give an '*All PD Studies*' population (comprising Studies 164, 165, 166, 167, 168, 169, 196, 228 and 248). Data from Study 105323 are not included in the '*All PD Studies*' group, as this is an ongoing blinded study, and limited data only are available; hence Study 105323 is reported separately.

**SPONSOR 120 DAY (4 MONTH) SAFETY UPDATE CONCLUSIONS**

At the cut-off dates for this 120-day Safety Update (16 November 2006 for data in the clinical trials database and 31 January 2007 for data in the OCEANS safety database), 3 clinical studies (Studies 196, 248 and 105323) were ongoing. The sponsor presented the new safety data and noted that new safety data from these ongoing studies have no impact on the prescribing information submitted as part of NDA 22-008 and no changes to the prescribing information are required.

**For the ongoing '*Open-Label Extension Studies*' combined (Studies 196 and 248), 7 new subjects were exposed to ropinirole CR for this reporting period. For the '*Ongoing Double-Blind Active Control Study*' (Study 105323), there were 114 new exposures to double-blind investigational product :**

· At the data cut-off of 16 November 2006 for this Safety Update, for '*All PD Studies*' combined (excluding Study 105323), 750 subjects were exposed to ropinirole CR and 479 (64%) subjects received ropinirole CR for more than a year. There was an even

distribution of subjects across the modal dose groups (≤8mg/day, 8-16mg/day, and >16mg/day) for exposure to ropinirole CR, with approximately one-third of subjects in each of the modal dose groups (36%, 31%, and 32%, respectively). Overall, 222 subjects received the maximum allowed dose of 24mg, with a total exposure of 63,329 patient-days.

· At the data cut-off of 16 November 2006 for this Safety Update, for the ongoing '*Open-Label Extension Studies*' combined, 502 subjects were exposed to ropinirole CR and 376 (79%) subjects received ropinirole CR for more than a year; 317 (63%) of the 502 subjects were ongoing. There was a smaller proportion of subjects in the modal dose group of ≤8mg/day (23%), compared to the modal dose groups of 8-16mg/day (37%) and >16mg/day (40%). Overall, 148 subjects received the maximum allowed dose of 24mg, with a total exposure of 50,807 patient-days.

· At the data cut-off of 16 November 2006 for this Safety Update, for the '*Ongoing Double-Blind Active Control Study*', Study 105323, 114 subjects had been randomized to receive double-blind investigational product (randomized in a 1:1 ratio to receive ropinirole CR or ropinirole IR).

**The sponsor noted that cumulative AE data from the ongoing clinical studies continue to support the conclusions reached in NDA 22-008. Ropinirole CR continues to be safe and well-tolerated :**

· At the data cut-off of 16 November 2006 for this Safety Update, the majority of subjects in the '*Open-Label Extension Studies*' reported at least one TEAE, with the highest incidence overall observed for Study 196 (98% for any event) compared to Study 248 (69% for any event). The higher reporting rates for TEAEs in Study 196 compared to Study 248 may be due to differences in visit schedule between these two studies. Clinic visits were conducted more frequently in Study 196 compared to Study 248.

· For Study 196, the most common TEAEs overall (excluding down-titration) (reported for ≥20% of subjects and excluding uncoded PTs) were peripheral edema (31%), headache (25%), nasopharyngitis (24%), back pain (23%), pain in extremity (22%), cough (22%), somnolence (20%) and nausea (20%). All of these common TEAEs were reported for a larger proportion of monotherapy subjects than adjunct therapy subjects.

· For Study 248, the most common TEAEs overall (excluding down-titration) (reported for ≥5% of subjects) were edema peripheral (7%), somnolence (7%), hallucination (7%), back pain (6%) and insomnia (5%). These common TEAEs were reported by a similar proportion of monotherapy subjects and adjunct therapy subjects, with the exception of hallucination, which was reported by more adjunct therapy subjects (8%) than monotherapy subjects (3%).

· At the data cut-off of 16 November 2006 for this Safety Update, for the '*Open-Label Extension Studies*' combined, the total cumulative proportion of subjects with a TEAE leading to discontinuation of study drug was 14% (69/502 subjects). Hallucination was the only TEAE leading to discontinuation of study drug that was reported by ≥2% of subjects. This event was reported for 9 (3%) subjects in the adjunct therapy population and 1 (<1%) subject in the monotherapy population, to give 10 (2%) subjects overall. In

addition, 3 (<1%) subjects had visual hallucination, 1 (<1%) subject had auditory hallucination and 1 (<1%) subject had mixed hallucinations leading to discontinuation of study drug.

· At the data cut-off of 16 November 2006 for this Safety Update, for the ongoing '*Double-Blind Active Control Study*', Study 105323, AEs leading to discontinuation of study drug were reported for 4 (4%) subjects (upper abdominal pain plus nausea, dyspepsia, intestinal obstruction, and depression).

· Overall the down-titration schedule for ropinirole CR was well-tolerated.

**SAE reports did not indicate any specific safety concerns with few SAEs considered by the reporting investigator to be related to ropinirole CR:**

· At the data cut-off of 16 November 2006 for this Safety Update, for the '*Open-Label Extension Studies*' combined, the cumulative incidence of TESAEs (excluding down-titration) for monotherapy subjects was 14% (28/194 subjects). The most common TESAEs were chest pain (8 subjects, 2%) and Parkinson's disease (7 subjects, 1%).

· At the cut-off of 31 January 2007 for the OCEANS safety database for this Safety Update, a cumulative total of 13 deaths have been reported for the 502 subjects in the ongoing '*Open-Label Extension Studies*'. None of the 13 deaths were considered by the reporting investigator to be related to treatment with investigational product. No deaths have been reported in the ongoing '*Double-Blind Active Control Study*', Study 105323.

**The incidence of events within AE topics of special interest did not raise any new safety concerns:**

· At the data cut-off of 16 November 2006 for this Safety Update, for the '*Open-Label Extension Studies*' combined, the most common topics of special interest for which events were judged to be possible or likely cases (≥2% of all subjects) were hallucination (61 subjects, 12%), fall/injury (47 subjects, 9%), hypotension (29 subjects, 6%), QTc prolongation and arrhythmia (12 subjects, 2%), compulsive behaviors consisting of pathological gambling and hypersexuality (9 subjects, 2%), and syncope (8 subjects, 2%).

**Vital sign changes in Study 196 were relatively minor, and unlikely to be of clinical significance:**

· At the data cut-off of 16 November 2006 for this Safety Update, mean absolute values for vital signs, for most extreme low and high values, were within the reference ranges for semi-supine and standing measurements. This finding was consistent for pulse, SBP and DBP.

· At the data cut-off of 16 November 2006 for this Safety Update, only a small number of subjects met the pre-specified criteria for severe systolic orthostatic hypotension ≥20mmHg (≤2% of subjects) or severe diastolic orthostatic hypotension ≥40mmHg (≤8% of subjects). The proportions of subjects meeting the pre-specified criteria for orthostatic hypotension were similar for visits at which a pre-dose assessment only was conducted, compared to visits at which both a pre-dose and post-dose assessment was conducted.

**Reviewer Comment**

- Overall, I agree with the sponsor that the data presented in the 120 Day (4 Month) Safety Update do not significantly change the safety profile of ER ropinirole that was suggested by data submitted in the original NDA submission.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

**Reviewer Comment**

- There were no new safety signals presented for a different safety profile than the one already recognized for immediate-release ropinirole. One limitation of the data was that it was not possible to assess the potential for dose-dependent TEAEs or any other safety parameter with ER ropinirole. This limitation is related to the fact there were no studies in which patients were randomized to fixed doses of ER ropinirole (vs placebo) to help characterize the dose-response curve for safety. The flexible dose titration pivotal trial (#169) that was conducted is not adequate for assessing a benefit to risk profile.

ER ropinirole is considered safe for approval.

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

**Reviewer Comment**

#### 7.4.1.1 Pooled data vs. individual study data

**Reviewer Comment**

- Although the sponsor presented pooled data analyses for many safety parameters and I presented some of these analyses in my review, generally, I focused my review primarily on analyzing individual study results because the study designs and populations were typically quite different across various studies.,

#### 7.4.1.2 Combining data

**Reviewer Comment**

- See my comment above for section 7.4.1.1.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for dose dependency for adverse findings

**Reviewer Comment**

- TEAEs (based upon our request) were analyzed for potential dose-dependency in study 169. The modal dose of ER ropinirole was determined and patients were categorized into 3 dose ranges and TEAEs in these dose ranges and "any dose" were analyzed for the incidence of TEAEs. Some TEAEs (i.e., dyskinesia, hypertension, fall) were thought to be dose-dependent and this information was noted in the label.

7.4.2.2 Explorations for time dependency for adverse findings

- Not-applicable

7.4.2.3 Explorations for drug-demographic interactions

The sponsor evaluated the frequency of TEAEs with respect to age, gender, and race. Overall, age and gender had no clinically meaningful effect on the tolerability of ropinirole CR based on an examination of the profile of TEAEs. Hallucinations were more common in elderly subjects treated with ropinirole CR vs non-elderly patients. TEAEs were more commonly reported in US populations than in Western Europe, which in turn reported higher rates compared to Eastern Europe. While studies did not include large numbers of Black Asian, or Hispanic subjects, the AE profiles in these subjects appear to be similar to that in White subjects.

7.4.2.4 Explorations for drug-disease interactions

The sponsor did not clearly conduct any analyses exploring drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

No patterns were observed with respect to concomitant medications, excepting entacapone, for which the frequency of hallucination was higher.

7.4.3 Causality Determination

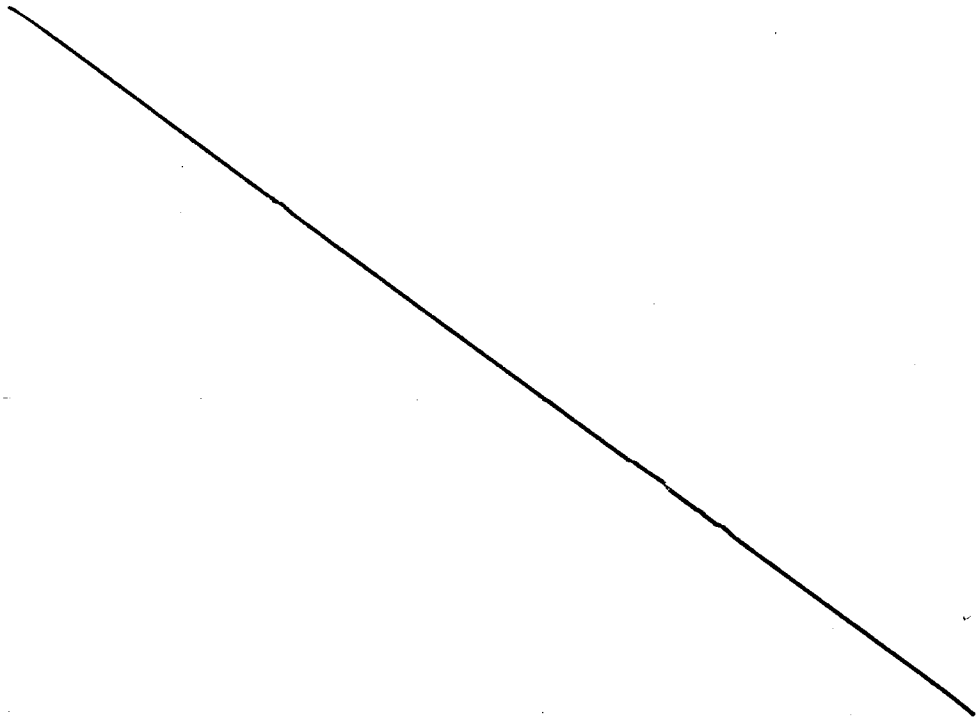
**Reviewer Comment**

- In general, I focused my assessment of attributing causality of ER ropinirole upon analyses of safety data that showed a greater frequency for ER ropinirole treatment vs that of placebo treatment in pivotal study 169.

# 8 ADDITIONAL CLINICAL ISSUES

## 8.1 Dosing Regimen and Administration

**The sponsor had recommended the following regimen for dosing and administration in its proposed label.**



b(4)

When REQUIP XL ——— is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be decreased gradually as tolerated. In — advanced Parkinson's disease study, the L-dopa dose was reduced once patients reached a dose of REQUIP XL ——— of 8 mg — day. Overall, L-dopa dose reduction was sustained in 93% of patients treated with REQUIP XL——— and in 72% of patients on placebo. On average the L-dopa dose was reduced by 34% in patients treated with REQUIP XL ——— *[see Clinical Studies (14)]*.

b(4)

REQUIP XL 24-HOUR should be discontinued gradually over a 7-day period.

**Switching From Immediate-release Ropinirole Tablets to REQUIP XL ———**
Patients may be switched directly from immediate-release ropinirole to REQUIP XL ——— Tablets. The initial dose of REQUIP XL——— should most closely match the total daily dose of immediate-release ropinirole, as shown in Table —

b(4)

**Table – Conversion from Immediate-release REQUIP to REQUIP XL ———** b(4)

| Immediate-release Ropinirole Tablets Total Daily Dose (mg) | REQUIP XL ——— Tablets Total Daily Dose (mg) |
|---|---|
| 0.75 to 2.25 | 2 |
| 3 to 4.5 | 4 |
| 6 | 6 |
| 7.5 to 9 | 8 |
| 12 | 12 |
| 15 to 18 | 16 |
| 21 | 20 |
| 24 | 24 |

Following conversion to REQUIP XL ———, the dose may be adjusted depending on therapeutic response (see section 2.2). b(4)

**The following is the dosing and administration that I have recommended and which was proposed in the label by the DNP.**

**Dosing for Parkinson's Disease**

The starting dose is 2 mg taken once daily for 1 to 2 weeks, followed by increases of 2 mg per day at 1 ———, depending on therapeutic response and tolerability, up to a maximally recommended dose of 24 mg per day. b(4)

In clinical trials, dosage was initiated at 2 ___ and gradually titrated ——— therapeutic response and tolerability. Doses greater than 24 mg/day have not been studied in clinical trials. Patients should be assessed for therapeutic response and tolerability at a minimal interval of 1 week or longer after each dose increment. Caution should be exercised during dose titration because too rapid a rate of titration can lead to dose selection that does not provide additional benefit, but that increases the risk of adverse reactions. *[see Clinical Studies (14.2)]* Due to the flexible dosing design used in clinical studies, specific dose response information could not be determined. b(4)

When REQUIP XL is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be decreased gradually as tolerated. In the placebo-controlled advanced Parkinson's disease study, the L-dopa dose was reduced once patients reached a dose of REQUIP XL of 8 mg per day. Overall, L-dopa dose reduction was sustained in 93% of patients treated with REQUIP XL and in 72% of patients on placebo. On average the L-dopa dose was reduced by 34% in patients treated with REQUIP XL *[see Clinical Studies (14)]*

REQUIP XL should be discontinued gradually over a 7-day period.

**Switching From Immediate-release Ropinirole Tablets to REQUIP XL**

Patients may be switched directly from immediate-release ropinirole to REQUIP XL Tablets. The initial dose of REQUIP XL should most closely match the total daily dose of the immediate-release formulation of REQUIP, as shown in Table 1.

**Table 1. Conversion from Immediate-release REQUIP to REQUIP XL**

| Immediate-release Ropinirole Tablets Total Daily Dose (mg) | REQUIP XL Tablets Total Daily Dose (mg) |
|---|---|
| 0.75 to 2.25 | 2 |
| 3 to 4.5 | 4 |
| 6 | 6 |
| 7.5 to 9 | 8 |
| 12 | 12 |
| 15 to 18 | 16 |
| 21 | 20 |
| 24 | 24 |

Following conversion to REQUIP XL, the dose may be adjusted depending on therapeutic response and tolerability (see —— 2.2). b(4)

### 8.2 Drug-Drug Interactions (DDIs)

Ropinirole drug interaction studies were conducted in support of the original application of ropinirole IR for the treatment of Parkinson's disease. No additional *in-vivo* drug interaction studies have been conducted for ropinirole CR, since the drug interaction potential for ropinirole CR is expected to be similar to that observed for ropinirole IR.

Some control release products are susceptible to dose dumping when administered with alcohol. *In-vitro* data have shown that ropinirole CR formulation is resistant to dose dumping in simulated gastric fluid with 24% v/v ethanol.

**Reviewer Comment**

- There is no new concern for ER ropinirole for DDIs.

### 8.3 Special Populations

**SAFETY IN SPECIAL GROUPS AND SITUATIONS**
Overall, there is increasing incidence of TEAEs with advancing age in all treatment phases, except for nausea which is more common in the Titration Phase among the younger than among the elderly, although the numbers of subjects are small.

In the All PD Studies analysis, subjects ≥65 years of age treated with placebo (68/113, 60%) or ropinirole CR (240/311, 77%) had a higher incidence of TEAEs compared to those 18 to 64 years (placebo: 36/78=46%, ropinirole CR: 204/302=68%) in these trials.

The overall incidence of TEAEs was generally similar between subjects ≥75 years of age (placebo: 27/43=63%, ropinirole CR=64/76=84%) and those ≥65 years of age, with some increases for isolated AEs in the ≥75 year group that do not appear to be clinically significant. Among subjects receiving ropinirole CR, hallucination was the only TEAE that occurred more commonly (>5% difference) in subjects ≥65 years compared to younger subjects. However, detailed comparisons by age in the All PD Studies analysis is confounded by unequal distributions of age across various studies, and specifically in Study 228, which excluded subjects >70 years. Therefore, only limited conclusions can be drawn from the combined analysis.

In the pivotal adjunctive therapy Study 169, TEAEs overall showed increasing incidence with increasing age in the placebo (18-64 years: 36/78=46%, ≥65 years: 68/113=60%) and ropinirole CR (18-64 years: 41/74=55%, ≥65 years: 88/128=69%) treatment groups.

Approximately 60% of subjects in this trial were ≥65 years (placebo: 113/191=59%, ropinirole CR: 128/202=63%), with 14% ≥75 years (placebo: 27/191=14%, ropinirole CR: 28/202=14%). The overall differences between ropinirole CR and placebo were less than 10% for the 18 to 64 years and ≥65 year subgroups, and were higher in the ≥75 year subgroup (43% placebo vs 80% ropinirole CR). Increased incidence in the very elderly was contributed to by a variety of TEAEs rather than a single, or small number of, preferred terms. Orthostatic hypotension, somnolence, and hallucination showed combined age and dose dependence that were highest in subjects ≥75 years. Study 228 (in which subjects >70 years were excluded per protocol) provides further support for the AE profile in the elderly, confirming that subjects ≥65 years (41/44=93%) had increased incidence of TEAEs on ropinirole CR compared to younger subjects (50/60=83%), with a lesser dependence on age seen in the Sinemet group (≥65 years: 42/51=82%, 18-64 years: 44/53=83%). Of note, in Study 228, age-dependent TEAEs covered a wide range of events, including many that are non-dopaminergic in character. Study 168 showed that the age-dependence of TEAEs is similar for the CR and IR formulations.

With respect to age, of the total number of subjects with PD in clinical studies of ropinirole CR, 52% (387/746) were 65 and over, while 14% (107/746) were 75 and over. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hallucinations (unreal visions, sounds, or sensations) have been reported in patients taking ropinirole CR and the risk is greater in patients with Parkinson's disease who are elderly.

With respect to gender, of the total number of subjects in clinical studies of ropinirole CR, 40% (297/746) were female, while 60% (449/746) were male.

Overall, TEAEs on ropinirole CR were more common in females than males (75% v 70%, respectively); these differences are not clinically meaningful. In the placebo group,

53% (33/62) of female subjects and 55% (71/129) of male subjects had TEAEs. No overall differences in safety were observed between sexes, and other reported clinical experience has not identified differences in responses between sexes.

While the number of subjects affected is small, it was noted that hypersexuality occurred exclusively in male subjects.

By-region analysis showed that, for Study 169, TEAEs were more common in the US, intermediate in Western Europe and lowest in Eastern Europe. This finding covered many system organ class groupings. Study 168 showed a similar by-region distribution to that in Study 169. These regional differences did not appear to be a result of different dose regimens or length of treatment in the different trials. TEAE reports in Study 228, representing a US population, were broadly similar to TEAE rates in the US subjects in Studies 168 and 169.

Concomitant medications generally did not affect the incidence of most TEAEs in a differential manner among the treatment groups. Concomitant treatment with entacapone was associated with a higher rate of hallucinations among subjects in Study 169. Among subjects in the ropinirole CR treatment group in Study 169 who also took entacapone, hallucination occurred in 13% (6/47) compared to 5% (11/202) in the population overall.

When combined with an additional case of visual hallucination, the overall incidence is 15% (7/47). Small numbers of subjects in each treatment group (Studies 169 and 228 combined) took estrogens (placebo N=2, ropinirole CR N=7, Sinemet N=5), CYP1A2 inhibitors (placebo N=6, ropinirole CR N=9, Sinemet N=4), or CYP1A2 inducers (placebo N=12, ropinirole CR N=32, Sinemet N=14), so no conclusions can be drawn from these results.

Overall, age and gender had no clinically meaningful effect on the tolerability of ropinirole CR based on an examination of the profile of TEAEs. Hallucinations were more common in elderly subjects treated with ropinirole CR. No patterns were observed with respect to concomitant medications, excepting entacapone, for which hallucination was higher. TEAEs were more commonly reported in US populations than in Western Europe, which in turn reported higher rates compared to Eastern Europe. While studies did not include large numbers of Black Asian, or Hispanic subjects, the AE profiles in these subjects appear to be similar to that in White subjects.

**Reviewer Comment**

- There is no new concern for treatment of any special population with ER ropinirole or reason for any specific comment.

### 8.4 Pediatrics

- Not applicable

### 8.5 Advisory Committee Meeting

- Not applicable

### 8.6 Literature Review

- Not applicable

### 8.7 Postmarketing Risk Management Plan

- Not applicable

### 8.8 Other Relevant Materials

- Not applicable

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The sponsor's conclusions are that ER ropinirole is safe and effective for approval for treatment of early and advanced Parkinson's Disease.

**Reviewer Comment**

- I concur with the sponsor's conclusions that ER ropinirole is safe and effective for approval for treatment of early and advanced Parkinson's Disease.

### 9.2 Recommendation on Regulatory Action

- I conclude that extended-release ropinirole (ER ropinirole , ropinirole XL, REQUIP XL) is safe and effective for the signs and symptoms of Parkinson's Disease (advanced and early).

**Effectiveness is based upon :**

**Reviewer Efficacy Conclusions for Study 169 (Randomized, Double-Blinded, Placebo-Controlled, Flexible Dose Titration Study of Adjunctive Treatment of Advanced Parkinson's Disease)**

- I conclude that ER ropinirole is superior to placebo as adjunctive treatment (to levodopa) of "off" and provides a statistically significant and noteworthy therapeutic benefit vs placebo in patients with advanced Parkinson's Disease for the primary analysis of the primary efficacy endpoints as well as other similar secondary analyses.

- The therapeutic benefit by which ER ropinirole treatment appeared to decrease "off" appeared to be related primarily to an increase in "on" without troublesome dyskinesia. This is a desirable goal of a drug developed to decreased "off" episodes.

- Although the dose range in the randomized, double-blinded, placebo-controlled, flexible dose-titration study was 2-24 mg, I am unable to conclude that the sponsor has demonstrated an optimal dosing regimen because dose-response was not characterized in a fixed, dose study in which patients were randomized to placebo or one of several fixed doses of ER ropinirole. In fact, I believe that results for studies 169 suggest that there is no clear suggestion of an additional clinical/therapeutic benefit of relatively higher daily doses of ER ropinirole (? > a mean dose of 8 or perhaps 14 mg/day depending on different analyses) which would be expected to increase the risk for the various and many types of toxicity from a dopaminergic drug. In study 168, the data suggest that there is no clear benefit for ER ropinirole (or IR ropinirole) above a mean dose of approximately 7-10 mg daily. I have outlined my concerns about excessive dosing in the Reviewer Comment section for efficacy results for studies 169 and 168.

- I am unable to conclude that an optimal titration schedule has been demonstrated for dosing ER ropinirole. Results from study 168 revealed that early Parkinson's Disease patients administered a slower and less aggressive rate of titration of IR ropinirole (than ER ropinirole) ultimately resulted in a much lower "optimal" dose of ropinirole (~ 50 %) than the "optimal" dose of ER ropinirole after a more aggressive, rapid titration rate. My reasons for this concern are outlined in the Reviewer Comment section discussing efficacy results for study168.

- There does not appear to be any concern about the efficacy of ER ropinirole with respect to the subgroup analyses for age or gender or country. Of note, ER ropinirole clearly appeared to be of therapeutic benefit to patients studied in the U.S.

- I conclude that it would be highly desirable to characterize the dose-response of ER ropinirole (and ideally also study and compare IR ropinirole) by requiring a phase 4 commitment for a fixed, dose study.

**Reviewer Efficacy Conclusions for Study 168 (Randomized, Double-Blinded, Comparator, Flexible Dose Titration Study of Monotherapy in Early Parkinson's Disease)**

- Overall, I conclude that ER ropinirole appears to show similar efficacy to IR ropinirole in patients with early Parkinson's Disease who were treated with either formulation as monotherapy and then "crossed-over" to the other formulation.

- Although the results suggested that ER ropinirole is statistically non-inferior to IR ropinirole, I believe that the margin (3 points for change from baseline for UPDRS motor score) selected for the non-inferiority is probably excessive. The point estimates of the primary efficacy endpoints are similar for ER ropinirole and IR ropinirole.

- I believe that the data results raise the question that there is little to no clear additional therapeutic benefit of dosing patients with relatively high daily doses of ropinirole (i.e. for both ER ropinirole and IR ropinirole) above 10 mg up to 24 mg. I have outlined my reasons for this concern in the Reviewer Comment section discussing efficacy results for study168. Results from study 169 (for advanced Parkinson's Disease) also raise the question that dosing at > 10-24 mg daily does not provide any clear therapeutic benefit.

- I believe that the relatively rapid titration rate/scheme for ER ropinirole (vs the slower rate of titration for IR ropinirole recommended in the label) increases the chance that patients will titrate to a higher dose of ER ropinirole that is not clearly beneficial but which may be associated with an increased risk for toxicity.

**Safety is based upon :**

- I conclude that ER ropinirole is safe for the treatment of signs and symptoms of Parkinson's Disease (advanced and early) as a result of my review of the safety findings submitted in this NDA for early and advanced Parkinson's Disease.

- Overall, the safety profile of ER ropinirole is similar to that for IR ropinirole which is approved for the treatment of signs and symptoms of Parkinson's Disease (advanced and early. I did not identify any adverse reactions that appeared to be unique to ER ropinirole.

- Quantitative differences in the frequency of certain adverse reactions between ER ropinirole and IR ropinirole seem more likely to be related to differences in the titration rate of ER ropinirole that is considerably more rapid and aggressive than the titration rate for IR ropinirole described in its label. Although there may be some quantitative differences in the frequency of adverse reactions related to the different shape of the pharmacokinetic (PK) profile for each formulation, I was not able to identify or suggest specific adverse reactions that may have been related to this PK difference. Overall, Cmax and AUC are similar for both formulations. The main difference is Tmax that is much longer (median 6-10 hrs) than the Tmax for IR ropinirole (~ 1-2 hours).

### 9.3 Recommendation on Postmarketing Actions

- I recommend that the sponsor conduct post-marketing studies to characterize the dose-response curves for efficacy and safety for ER ropinirole in advanced and

early Parkinson's Disease. This could be accomplished by conducting 2 randomized, double-blinded, placebo-controlled, parallel, fixed dose studies in early and advanced Parkinson's Disease.

Ideally, I believe that 5 fixed doses (? 2, 4, 8, 12, 24 mg/day) of ER ropinirole should be included in each study for comparison with placebo to attempt to identify the lowest effective dose and the lowest, maximally therapeutic dose.

It might also be desirable that multiple, fixed doses of IR ropinirole also be evaluated in these same studies to characterize the dose-response for IR ropinirole. However, it is not clear that this is necessary because our impression is that the same total dose of IR-ropinirole is essentially bioequivalent to ER ropinirole.

9.3.1 Risk Management Activity

- Not applicable. There is no risk management plan.

9.3.2 Required Phase 4 Commitments

- See section 1.2 for my recommendation for Phase 4 Commitments

9.3.3 Other Phase 4 Requests

- Not applicable

### 9.4 Labeling Review

- Draft labeling by the DNP was sent to the sponsor and is not shown in this review. Final labeling was not able to be negotiated with the sponsor prior to the PDUFA date.

### 9.5 Comments to Applicant

- Draft labeling by the DNP was sent to the sponsor and is not shown in this review.

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

- Not applicable other than the individual study reports that were described in section 6 (Integrated Review of Efficacy)

### 10.2 Line-by-Line Labeling Review

- The line-by-line labeling review was conducted separately from this review and is not presented here.

## REFERENCES

- Not applicable

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Norman Hershkowitz
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