Efficacy and Safety Profiles of Pramipexole Extended-Release for Parkinson Disease

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CNE Surabaya, May 23, 2010
Neurotransmitter balance in Normal and Dopamine-depleted brain

Normal:

- Glutamate
- Acetylcholine

DA (D2)

Parkinsonism:

- Glutamate
- Acetylcholine

DA (D2)

Akinesia

Movement

Direct Path

Indirect Path

DA (D1): excitatory
D2: inhibition
Dopamine Receptor Subtypes

<table>
<thead>
<tr>
<th>D1-like receptors</th>
<th>D2-like receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁</td>
<td>D₂</td>
</tr>
<tr>
<td>D₅</td>
<td>D₃</td>
</tr>
<tr>
<td></td>
<td>D₄</td>
</tr>
</tbody>
</table>

Poewe W. In: *Principles of Treatment in Parkinson’s Disease;* 2005.
D$_3$ Receptors in Brain Distribution

D$_3$ receptors in the mesolimbic dopaminergic system may be involved in mood and behaviour.

“Motor area” - D$_3$ receptors potential therapeutic target

Caudate nucleus
Accumbens
Amygdala

Putamen
Ventral tegmental area
Substantia nigra

D$_3$ receptors in the mesolimbic dopaminergic system may be involved in mood and behaviour.

Challenges in Treating PD

- Motor symptoms
- Non-motor symptoms
- Disease progression
- Motor complications: “wearing off”, “on-off”, dyskinesia
- Drug safety and tolerability
- Adherence to treatment

Types of Motor Complications in PD

- Motor fluctuations
  - Wearing-off
  - Delayed "on"
  - No "on"
  - "On/off"
Putative Pathophysiology of Motor Complications in PD

- Striatal dopaminergic denervation
- Priming of striatal dopamine receptors
- Pulsatility of drug administration and subsequent receptor stimulation

Non-Motor Symptoms of PD

Neuropsychiatric symptoms
- Depression, anxiety, panic attacks, hallucinations, psychosis, cognitive impairment

Sleep disorders
- REM sleep behaviour disorder (RBD), excessive daytime somnolence, sleep apnoea, restless legs syndrome (RLS) and periodic limb movements

Autonomic symptoms
- Bladder function, sweating, orthostatic hypotension, impotence

Digestive system symptoms
- Swallowing difficulties and constipation

Sensory Symptoms
- Pain and olfactory dysfunction
- Visual disturbances

Other symptoms
- Fatigue, gait and balance disturbances

Symptomatic Treatment of Motor Symptoms in PD

Abbreviations: DDC, dopa decarboxylase; TH, tyrosine hydroxylase; L-DOPA, levodopa; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; COMT, catechol-O-methyltransferase; D, dopamine receptors; 3-OMD, 3-O-methylldopa

Motor Symptoms in PD
Symptomatic Treatment

Levodopa
- Decarboxylase inhibitors: benserazide, carbidopa
- Cathechol-O-methyltransferase (COMT) inhibitors: entacapone, tolcapone

Dopamine agonists
- Non-ergots: pramipexole, ropinirole, rotigotine, apomorphine
- Ergots: bromocriptine, cabergoline, lisuride, pergolide

Monoamine oxidase (MAO)-B inhibitors
- selegiline, rasagiline

Non-dopaminergic drugs
- Anticholinergics: benzhexol, trihexyphenidyl
- Glutamate antagonist: amantadine

Dopamine Agonists in PD

**Pharmacological Advantages**

- Direct dopamine receptor stimulation
- No need for metabolic conversion to dopamine
- Activity independent from other metabolic pathways (catechol-O-methyltransferase, monoamine oxidase)
- Not reliant on presynaptic storage in dopaminergic terminals
- Long half life ➔ more continuous stimulation of dopamine receptors
- Specific for dopamine receptor subtypes ($D_2/D_3$) less likely to induce dyskinesia via $D_1$ receptor activity

Poewe W. In: *Principles of Treatment in Parkinson’s Disease*; 2005.
Non-Ergot Dopamine Agonists in the Treatment of PD

**First-line therapy in early PD**

- Potential to provide control of motor symptoms for several years
- Low incidence of motor complications
- Delay the use of levodopa and related motor complications
- Pramipexole has been shown to reduce depressive symptoms
- May modify clinical disease progression
- Favourable safety profile
- Generally well tolerated

Receptor Interactions

Non-ergot agonists
• Selective for dopamine receptors
• Selective for D2-like receptor family
• No interaction with D1-like receptors (except apomorphine)

Ergot agonists
• Non-selective
• Act on noradrenergic and serotonergic receptors
• No selectivity for dopamine receptor subtypes

Response to Levodopa and Evolution of Motor Complications

- Long duration motor response
- Low incidence of dyskinesias
- Shorter duration motor response
- Increased incidence of dyskinesias
- Short duration motor response
- “On” time consistently associated with dyskinesias

Pramipexole may act as Neuroprotective

• Reduction of oxidative stress
• Reduction of glutamatergic excitotoxicity
• Reduction mitochondria dysfunction & apoptosis
• Reduction ubiquitin/proteosom dysfunction
• Reduction of inflammation-induced neuronal death
• Promotion of neurotrophic factors
• Promotion dopamine-neuron genes
• Promotion neurogenesis
Dopaminergic Drug Delivery in PD: What Are the Challenges?

- Continuous vs. discontinuous delivery
- Multiple daily doses → pill burden
- Patient convenience
- Patient compliance
  - total adherence
  - timing adherence
Continuous Drug Delivery (CDD)

- Physiological stimulation of striatal dopamine receptors is generally continuous and tonic
- Dopaminergic tone is lost in PD
- Pulsatile stimulation by short-acting drugs such as levodopa may contribute to motor complications
- Longer-acting dopamine agonists such as pramipexole contribute to more continuous dopaminergic stimulation and lower the incidence of motor complications compared to levodopa

Continuous Drug Delivery and PD

- Levodopa plus catechol-O-methyltransferase (COMT) inhibitor
- Intrajejunal administration-levodopa
- Transdermal administration – rotigotine, lisuride
- Subcutaneous infusion – apomorphine
- Extended-release preparations – pramipexole, ropinirole

Pramipexole Extended Release

Results of Phase I and Phase III Trials
Pramipexole Extended Release

Overview of Trials

- 5 Phase I trials (completed):
  - 152 male and female healthy volunteers (HVs)
  - Of these, 142 HVs received a single dose (ER) or multiple doses of pramipexole IR
  - Confirmed bioequivalence between pramipexole IR and ER formulations

- 3 international Phase III double-blind trials (completed):
  - 1212 patients treated

- Long-term open-extension international Phase III trials (on-going):
  - 902 patients treated with pramipexole ER
Plasma Concentration Time Profiles for Pramipexole ER and IR

Less frequent plasma level fluctuations with 4.5 mg pramipexole ER once daily compared to 1.5 mg pramipexole IR thrice daily.

Dansirikul C, et al. 18th Meeting of the Population Approach Group, St. Petersburg, Russia, June 23-26, 2009; Abstract 1532
### Pramipexole Extended Release

**International Phase III Double-Blind Trials**

**Number of patients included**

<table>
<thead>
<tr>
<th></th>
<th>Pramipexole ER</th>
<th>Pramipexole IR</th>
<th>Placebo</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EARLY</strong></td>
<td>223</td>
<td>213</td>
<td>103</td>
<td>539</td>
</tr>
<tr>
<td><strong>ADVANCED</strong></td>
<td>164</td>
<td>175</td>
<td>178</td>
<td>517</td>
</tr>
<tr>
<td><strong>SWITCH</strong></td>
<td>104</td>
<td>52</td>
<td>-</td>
<td>156</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>491</td>
<td>440</td>
<td>281</td>
<td>1212</td>
</tr>
</tbody>
</table>

Pramipexole Extended Release in Early PD

Design

599 enrolled / 539 entered / 539 treated / 2:2:1 randomization

- Pramipexole ER \((n = 223)\)
- Pramipexole IR \((n = 213)\)
- Placebo \((n = 103)\)

- Double-blind, double-dummy, placebo-controlled, randomized, parallel group trial
- Flexible up-titration from 0.375 to 4.5 mg/day over 7 weeks, then maintenance phase 26 wks.
- Levodopa allowed as a rescue medication, during maintenance phase

Pramipexole Extended Release in Early PD

Objectives

At Week 18:
- To demonstrate superiority of pramipexole ER vs. placebo

At Week 33:
- To demonstrate non-inferiority of pramipexole ER vs. pramipexole IR
- To demonstrate maintenance of efficacy over 33 weeks

# Pramipexole Extended Release in Early PD

## Main Efficacy Endpoints

<table>
<thead>
<tr>
<th>Primary</th>
<th>UPDRS II+III score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key secondary</strong></td>
<td>% Clinical Global Impression–Improvement (CGI-I) and Patient Global Impression–Improvement (PGI) responders</td>
</tr>
</tbody>
</table>
Pramipexole Extended Release in Early PD

Safety Endpoints

• Incidences of adverse events
• Proportions of withdrawals due to adverse events
• Vital signs and weight
• Epworth Sleepiness Scale (ESS)
• Modified Minnesota Impulsive Disorders Interview (mMIDI): subscales for pathological gambling, compulsive buying, compulsive sexual behaviour
• Safety laboratory tests
Pramipexole Extended Release in Early PD

Higher CGI-I and PGI-I Responder Rates vs. Placebo at Week 18*

Responders = “very much” or “much improved”, Clinical Global Impression–Improvement (CGI-I); “better”, Patient Global Impression–Improvement (PGI-I).

* With post-levodopa-rescue data censored.

Pramipexole Extended Release in Early PD

Comparison of Levodopa Rescue vs. Placebo at Week 33

Pramipexole Extended Release in Early PD
Not Inferior to Pramipexole Immediate Release at Week 33*

* FAS (LOCF) with post-levodopa-rescue data censored

Non-inferiority was demonstrated between pramipexole ER and IR at Week 33

Pramipexole Extended Release in Early PD

Significant Decrease in UPDRS II+III Over Time up to Week 33

Pramipexole extended release and immediate release offered a stable improvement over time.
### Pramipexole Extended Release in Early PD

**Most Frequent Adverse Events at Week 33**

AEs with frequency greater than with placebo and ≥5% in any pramipexole group

<table>
<thead>
<tr>
<th></th>
<th>Placebo N (%)</th>
<th>Pramipexole ER N (%)</th>
<th>Pramipexole IR N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated</td>
<td>103</td>
<td>223</td>
<td>213</td>
</tr>
<tr>
<td>Patients with any AE</td>
<td>80 (77.7)</td>
<td>189 (84.8)</td>
<td>172 (80.8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15 (14.6)</td>
<td>81 (36.3)</td>
<td>70 (32.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (8.7)</td>
<td>48 (21.5)</td>
<td>51 (23.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (1.9)</td>
<td>32 (14.3)</td>
<td>25 (11.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (6.8)</td>
<td>26 (11.7)</td>
<td>25 (11.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (3.9)</td>
<td>14 (6.3)</td>
<td>12 (5.6)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (1.0)</td>
<td>12 (5.4)</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>4 (3.9)</td>
<td>12 (5.4)</td>
<td>18 (8.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (5.8)</td>
<td>7 (3.1)</td>
<td>15 (7.0)</td>
</tr>
</tbody>
</table>

No relevant difference was observed between the two pramipexole formulations.

Conclusion Efficacy

18-week analysis:

• Superiority of pramipexole ER vs. placebo was demonstrated at Week 18 for both the primary endpoint (UPDRS II+III) and the key secondary endpoints (CGI-I and PGI-I)

33-week analysis:

• Non-inferiority of pramipexole ER vs. pramipexole IR was demonstrated at Week 33

• Maintenance of efficacy was shown after 33 weeks of treatment

The safety and tolerability of pramipexole ER was comparable to pramipexole IR, at similar mean daily dose and dose distribution, and comparable duration of treatment.
Pramipexole Extended Release in Advanced PD

**Design**

605 enrolled / 518 entered / 517 treated /

- Pramipexole ER ($n = 165$)
- Pramipexole IR ($n = 175$)
- Placebo ($n = 178$)

- Double-blind, double-dummy, placebo-controlled, randomized, parallel group
- Flexible up-titration from 0.375 to 4.5 mg/day over 7 weeks (dose to be increased in all patients who were not at least “a little better” on the Patient Global Impression–Improvement (PGI-I), then maintenance phase.
- Concomitant levodopa could be reduced in case of dopaminergic adverse events

Pramipexole Extended Release in Advanced PD

Objectives

• To demonstrate superiority of pramipexole ER vs. placebo on UPDRS II+III (primary endpoint) and “off” time (key secondary endpoint) at Week 18 (confirmatory analysis)

• To demonstrate maintenance of efficacy at 33 weeks (descriptive analysis)

• To compare pramipexole ER and pramipexole IR efficacy (descriptive comparison, no formal statistical non-inferiority test)

Pramipexole Extended Release in Advanced PD

Efficacy Endpoints

<table>
<thead>
<tr>
<th>Primary</th>
<th>- UPDRS II+III score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key secondary</td>
<td>- Percentage “off” time</td>
</tr>
</tbody>
</table>

Pramipexole Extended Release in Advanced PD

Safety Endpoints

- Incidence of adverse events
- Proportion of withdrawals due to adverse events
- Vital signs and weight
- Epworth Sleepiness Scale (ESS)
- Modified Minnesota Impulsive Disorders Interview (mMIDI): subscales for pathological gambling, compulsive buying, compulsive sexual behaviour
- Safety laboratory tests
Pramipexole Extended Release in Advanced PD

Significant UPDRS II+III Score Change vs. Placebo at 18 Weeks

* $P = 0.0001$ pramipexole ER vs. placebo
† $P < 0.0001$ pramipexole IR vs. placebo

Pramipexole Extended Release in Advanced PD

Most Frequent Adverse Events at Week 18

Adverse events (AEs) more than with placebo and ≥5% in any pramipexole group

<table>
<thead>
<tr>
<th></th>
<th>Placebo n (%)</th>
<th>Pramipexole ER n (%)</th>
<th>Pramipexole IR n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated</td>
<td>178</td>
<td>164</td>
<td>175</td>
</tr>
<tr>
<td>Patients with any AE</td>
<td>99 (55.6)</td>
<td>90 (54.9)</td>
<td>112 (64.0)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>14 (7.9)</td>
<td>27 (16.5)</td>
<td>32 (18.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>24 (13.5)</td>
<td>18 (11.0)</td>
<td>24 (13.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (10.1)</td>
<td>18 (11.0)</td>
<td>20 (11.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (2.8)</td>
<td>11 (6.7)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (5.1)</td>
<td>11 (6.7)</td>
<td>10 (5.7)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>1 (0.6)</td>
<td>9 (5.5)</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (5.1)</td>
<td>8 (4.9)</td>
<td>18 (10.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (2.8)</td>
<td>2 (1.2)</td>
<td>10 (5.7)</td>
</tr>
</tbody>
</table>

- The AE profile was similar between ER and IR groups
- Less AEs reported in the ER group than in placebo and IR groups

Pramipexole ER in Advanced PD

Conclusion Efficacy

• Superiority of pramipexole ER vs. placebo was demonstrated at Week 18 for both the primary endpoint (UPDRS II+III) and the key secondary endpoint (“off” time)

• Maintenance of efficacy was shown after 33 weeks of treatment

• The efficacy of pramipexole ER was comparable to pramipexole IR, at similar mean daily dose, dose distribution, and comparable duration of treatment

Pramipexole was well tolerated overall, with a similar occurrence of adverse events (AEs) at 18 weeks in the pramipexole ER group (54.9%) compared to placebo (55.6%) and a numerically lower percentage of AEs compared to pramipexole IR (64%).
Pramipexole Extended Release in PD

General Considerations

• Treatment convenience and compliance:
  – Pramipexole ER given once a day is more convenient than pramipexole IR t.i.d. and therefore may increase treatment compliance, which may result in optimised efficacy and tolerability
  – Reduction of pill burden and decrease of erratic drug intake are key success factors in PD treatment

• The psychological impact of a once-daily dosing regimen in de novo PD patients
  – Newly diagnosed PD patients may experience more ease in coping with their illness via a simpler, once-daily dosing regimen
Clinical fluctuation in PD and management (1)

1. Wearing off
   - More frequent dosing of levodopa
   - Add DA agonist
   - Controlled release levodopa
   - Add COMT inh

2. Delayed onset of response
   - Ensure L Dopa not given with protein (low protein diet)
   - Give before meal
   - Melted with bicarbonate water
Clinical fluctuation in PD and management

3. Off period dystonia
- Increase dose of L-dopa
- Increase dose frequency
- Give before meals
- Add COMT inh/DA agonist

4. On-off phenomenon
- Sustained released DA agonist
- Liquid levodopa
- Clozapine

5. Peak-dose dyskinesia
- Decrease each dose of L-dopa
- Stop adjunctive medication that potentiate with Levodopa
- Add DA agonist
- Add Amantadine
- Add anticholinergic
Clinical fluctuation in PD and management (3)

- Morning dystonia
  - Give morning dose earlier
  - Add DA agonist
  - Lithium, Baclofen (?)

- Nocturnal myoclonus
  - Stop evening dose of levodopa
  - Add Clonazepam
  - Tricyclic antidepressant (?)

- Hallucination
  - Stop anticholinergic
  - Stop amantadine
  - Reduce dose/stop of DA agonist
  - Add Thioridazine/selective cortical DA antagonist (i.e. Clozapine)
Thank YOU
Pramipexole Extended Release

Switch Trial in Early PD

• Double-blind, double-dummy, active-controlled, randomized, parallel group

• Two treatment arms: pramipexole ER and pramipexole IR (2:1 ratio)

• Overnight switch from pramipexole IR (open label) to pramipexole ER or pramipexole IR (double blind)

• Dose adaptation allowed at Week 4 and 5

• Final assessment at Week 9

Pramipexole Extended Release Switch Trial in Early PD

**Design**

Phase: Run-in → Switch → Maintenance → Taper

- **ER (DB)**
- **IR (OL, ≥1.5 mg/d)**
- **IR (DB)**

Optional 1-level dosage adjustments

Weeks: -4 to 10

Visits: 1, 2, 3, 4, 5, 6

Although a large majority of patients (84.5%) successfully switched overnight from IR to ER, non-inferiority between both formulations was not formally demonstrated.

Pramipexole Extended Release Switch Trial in Early PD

Objectives

• To assess if patients with early PD can be successfully switched* (overnight) from pramipexole IR to pramipexole ER

• To establish if this “successful switch” can be obtained with or without dose adaptation

• To provide information about the dose conversion ratio (mg:mg) from pramipexole IR to pramipexole ER

Definition of “successful switch” = No worsening of the UPDRS II+III score by more than 15% from baseline and no discontinuation due to a drug-related adverse event

Metabolic Pathways of Dopamine and L-dopa

L-Tyrosine → 3-O-Methyltransferase (COMT) → 3-OMD → DDC → Dopa Decarboxylase (DDC) → L-Dopa → Monoamine Oxidase (MAO) → Dopamine

Dopamine → COMT → 3-Methoxytyramine → HVA → COMT → DOPAC → MAO → 3,4 Dihydroxyphenylacetaldehyde

Other metabolic pathways

COMT = Catechol-O-methyltransferase, DDC = Dopa decarboxylase, DOPAC = 3,4-dihydroxyphenylacetic acid, HVA = homovanillic acid, MAO = Monoamine oxidase, 3 OMD = 3-O-methyldopa
Pramipexole Extended Release in PD

Conclusions (1)

• In Phase I trials:
  – Bioequivalence was demonstrated on all relevant pharmacokinetic parameters between pramipexole extended release (ER) q.d. (once daily) and pramipexole immediate release (IR) t.i.d. (thrice daily), at steady-state, in fasted conditions
  – Pramipexole ER q.d. provides less frequent plasma level fluctuations compared to pramipexole IR t.i.d.
  – Pramipexole ER can be administered with or without food

• In the Early PD Phase III trial:
  – Superiority of pramipexole ER vs. placebo was demonstrated at Week 18, and maintenance of efficacy was observed at Week 33
  – Non-inferiority of pramipexole ER vs. pramipexole IR was demonstrated at Week 33, at similar mean daily dose, dose distribution, and comparable duration of treatment
Main Inclusion Criteria

- Male and female patients with idiopathic early Parkinson’s disease (PD) diagnosed within 5 years
- Modified Hoehn & Yahr: I to III
- Total previous exposure to levodopa not longer than 3 months
- Not currently receiving levodopa or dopamine agonist
- Concomitant anti-PD treatments with monoamine oxidase B (MAO-B) inhibitors, amantadine, or anticholinergics were allowed, provided the dose was stable for at least 4 weeks prior to baseline
Phase I Multiple Rising Dose Trial

Study Design

0.375 mg ER q.d.

0.75-3.75 mg ER q.d.

5 days

21-23 days

5 days

5 days

5 days

3 x 1.5 mg IR fasted

4.5 mg ER q.d. fed

4.5 mg ER q.d.* fasted

4.5 mg ER q.d. fasted

4.5 mg ER q.d. fasted

4.5 mg ER q.d. fasted

3 x 1.5 mg IR fasted

3 x 1.5 mg IR fasted

3 x 1.5 mg IR fasted

0.375 mg ER q.d.: once daily

Maintained pramipexole monotherapy treatment in early PD results in significantly lower dyskinesia rates compared to levodopa.

What is wearing off phenomenon?

Wearing off vary from person to person,
Wearing off correlate with pharmacokinetics of levodopa,
On-off require additional pharmacodynamic, including sensitisation of dopaminergic receptors.
# Dopamine Agonists

## Dosing and Bioavailability

<table>
<thead>
<tr>
<th></th>
<th>Levodopa</th>
<th>Ropinirole IR</th>
<th>Ropinirole ER</th>
<th>Pramipexole IR</th>
<th>Pramipexole ER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Commonly used daily dosage (mg/d)</strong></td>
<td>Up to 1200</td>
<td>3–24</td>
<td>4–24</td>
<td>0.375–4.5 (salt)</td>
<td>0.375–4.5 (salt)</td>
</tr>
<tr>
<td><strong>Commonly used dosing frequency</strong></td>
<td>3–8</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Oral bioavailability, %</strong></td>
<td>99%</td>
<td>50</td>
<td>50</td>
<td>&gt;90</td>
<td>&gt;90</td>
</tr>
<tr>
<td><strong>Elimination t1/2, h</strong></td>
<td>1.5</td>
<td>6</td>
<td>6</td>
<td>8–12</td>
<td>8–12*</td>
</tr>
</tbody>
</table>

The prolonged duration of action of extended-release (ER) formulations is related to their extended absorption: $T_{max} = 6$–$8$h vs. 1–2h for pramipexole ER vs. immediate release (IR), respectively.

Poewe W. In: *Principles of Treatment in Parkinson’s Disease*; 2005.
Summary of Product Characteristics