NEW TREATMENTS IN PARKINSON'S

BIJU MOHAMED
Objectives

- Safinamide
- Opicapone
- PD Psychosis treatment
- Newer methods of L-dopa delivery
- Repurposing old drugs
- Non Oral treatments
Mr R

- 72, IPD for 7 years, mixed type
- Initiated on MAOBI,
- Progressive symptoms, L-dopa started
- Troubling ‘off’ symptoms and wearing off
Mr R,

- MAOB I stopped
- Converted to Stalevo, 125 (5 times a day), mild dyskinesia's,
- Sleep problems, some features of restless legs
- Rotigotine patch initiated

■ However continues to experience poor motor control with dyskinesia's
■ Continues to attend clinic
SAFINAMIDE
Multiple pharmacological systems are affected by safinamide, involving:

- **Dopaminergic targets**
  - Monoamine oxidase B (MAO-B)

- **Non dopaminergic targets**
  - Sodium channels
  - Calcium channels
  - Glutamate release

- **Reversible** – non-covalent binding
- **Highly specific** – 5,000 greater affinity for the form B vs form A of MAO shown in animal studies
- **Potent** (nMolar range) – full inhibition of platelet MAO-B was found in humans at doses below the lowest clinical dose

Ref: Caccia, C; Maj, R; Calabresi, M; Maestroni, S; Faravelli, L; Curatolo, L; Salvati, P; Fariello, RG
"Safinamide: From molecular targets to a new anti-Parkinson drug".
Neurology., 2006; 67(7 Suppl 2): S18–23.67
Study 016/018: Design
(double-blind, placebo controlled study through 2 years)

- **Study 016**
  - Primary endpoint: ON-time
  - 6 months: 669 patients
  - 18 months: 544 patients

- **Study 018**
  - Primary endpoint: Dyskinesia Rating Scale (DRS)
  - 18 months: 544 patients

Study 016: Inclusion & exclusion criteria

Inclusion:

- Aged 30–80yrs with mid to late stage PD, experiencing motor fluctuations while receiving L-dopa and other dopaminergic treatments
- Idiopathic PD of ≥3yrs duration
- Hoehn and Yahr stage I-IV during off
- Motor fluctuations (>1.5 hours’ off time/day)
- Patients had to be able to accurately maintain a diary.

Exclusion:

- Patients with late-stage PD were excluded if they experienced severe, disabling peak-dose or biphasic dyskinesia, or unpredictable or widely swinging symptom fluctuations
- Patients with evidence of dementia, major psychiatric illnesses, retinal disease and/or severe and progressive medical illnesses were excluded.
Study 016: End points

Primary End Point:
- Change in mean daily total on time with no or non-troublesome dyskinesia recorded in patient diaries

Secondary End Points:
- Total daily off time
- Unified Parkinson’s Disease Rating Scale (UPDRS) Part III (motor) scores during on
- Clinical Global Impression-Change (CGI-C) scores
- Off time following the first morning L-dopa dose
- Dyskinesia Rating Scale (DRS) scores during on time
- UPDRS Part II (activities of daily living) scores during on
- Clinical Global Impression-Severity (CGI-S) scores
- Percentage change in L-dopa dose.
Study 016: Primary efficacy variable  
(mean change in total daily ON* time)
Study 016: Results Summary

- Significant increase in mean total ‘on time with no or non-troublesome dyskinesia’ versus placebo in both the safinamide 50 mg/day (0.51 hours; P=0.0223) and 100 mg/day (0.55 hours; P=0.0130)

- Both doses showed significant improvements in off time following the morning L-dopa dose compared with placebo (-0.6h 100mg/day p=0.0011, -0.5h 50mg/day p=0.0031)
Study 018: Endpoints

Primary End Point:
- Mean change from baseline (at Study 016 start) of the total score of the Dyskinesia Rating Scale (DRS) during ON time

Secondary End Points:
- Mean change from baseline to endpoint in diary ON time without troublesome dyskinesia
- Diary responder rates and change in diary categories
- UPDRS Part II, III, IV
- Change in L-dopa dose
- Clinical Global Impression—Change (CGI-C), Clinical Global Impression-Severity (CGI-S)
Study 018: Principal secondary endpoint
*(mean change in Total daily ON time)*

Graph adapted from: Borgohain et al: Two-Year, Randomized, Controlled Study of Safinamide as Add-on to Levodopa in Mid to Late Parkinson’s Disease. Movement Disorders Movement Disorder. 2014 Sep;29(10):1273-80
Summary of Adverse Events in the combined Study 016 & Study 018 safety population

<table>
<thead>
<tr>
<th>Adverse Event Category, n (%)</th>
<th>Placebo (n = 175)</th>
<th>Safinamide 50 mg/d (n = 189)</th>
<th>Safinamide 100 mg/d (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>160 (91.4)</td>
<td>168 (88.9)</td>
<td>163 (90.6)</td>
</tr>
<tr>
<td>Newly emergent during Study 018</td>
<td>149 (85.1)</td>
<td>145 (76.7)</td>
<td>141 (78.3)</td>
</tr>
<tr>
<td>Re-emergent during Study 018</td>
<td>21 (12.0)</td>
<td>18 (9.5)</td>
<td>19 (10.6)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>28 (16.0)</td>
<td>32 (16.9)</td>
<td>34 (18.9)</td>
</tr>
<tr>
<td>Discontinuation due to TEAEs</td>
<td>10 (5.7)</td>
<td>10 (5.3)</td>
<td>12 (6.7)</td>
</tr>
<tr>
<td>Most frequent TEAEs (occurring in ≥5% of patients in any group)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening of Parkinson’s disease</td>
<td>42 (24.0)</td>
<td>42 (22.2)</td>
<td>43 (23.9)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>38 (21.7)</td>
<td>59 (31.2)</td>
<td>50 (27.8)</td>
</tr>
<tr>
<td>Cataract</td>
<td>27 (15.4)</td>
<td>27 (14.3)</td>
<td>25 (13.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>21 (12.0)</td>
<td>17 (9.0)</td>
<td>12 (12.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>21 (12.0)</td>
<td>14 (7.4)</td>
<td>21 (11.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 (12.0)</td>
<td>22 (11.6)</td>
<td>15 (8.3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (6.3)</td>
<td>21 (11.1)</td>
<td>13 (7.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (7.4)</td>
<td>20 (10.6)</td>
<td>15 (8.3)</td>
</tr>
<tr>
<td>Fall</td>
<td>17 (9.7)</td>
<td>20 (10.6)</td>
<td>15 (8.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (6.9)</td>
<td>19 (10.1)</td>
<td>18 (10.0)</td>
</tr>
</tbody>
</table>

TEAE, treatment-emergent adverse event.
Study 018: Summary

- Both safinamide doses **improved ON time without troublesome dyskinesia** when used as an add-on to L-dopa in these PD patients with motor fluctuations, despite optimized PD therapy as shown by patient diary data.

- Improvements seen at 6 months were still present at the end of the study, showing that safinamide, especially at a dose of 100 mg/d, remains more effective than placebo after 2 years of treatment.

Clinical benefits include improvements in:

- Motor function
- Activities of daily living
- Depressive symptoms
- Patients’ clinical status
- Quality of life, including:
  - Activities of daily living
  - Emotional well-being
  - Communication
  - Bodily discomfort.
SETTLE Study: Design

- Starting dose: 50 mg daily
- After two weeks (at day 14), the dose was increased to 100 mg daily

Schapira et al; Movement Disorder Society 14th International Congress, Buenos Aires, Argentina, 13-17 June 2010 Poster 378
SETTLE: Inclusion & exclusion criteria

**Inclusion**
- Male or female aged 30-80 years
- Diagnosis of idiopathic PD (>3yrs duration)
- Hoehn and Yahr Stage I–IV (during OFF state)
- Stable doses of levodopa with 1.5 hours’ OFF time per day.

**Exclusion**
- Severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations
- Psychosis, depression (GRID Hamilton Rating Scale for Depression–17-item [GRID HAM-D] 17), dementia, or cognitive dysfunction
- Treatment with monoamine oxidase inhibitors.
SETTLE: Endpoints

Primary efficacy*
- Daily ON time without troublesome dyskinesia

Secondary efficacy*
- UPDRS Part II (ADL) during ON phase
- Cogtest®PD battery *(see Key features)*
- Dyskinesia Rating Scale during ON phase
- CGI-S
- Proportion of patients with an improvement (score of 1, 2, or 3) on CGI-C
- CGI-C
- UPDRS Part III (motor examination) during ON phase
- Daily OFF time
- Daily OFF time following morning levodopa dose
- Change in levodopa dose
- EQ-5D™
- PDQ-39
- Patient’s Global Impression of Change
SETTLE Study: Primary efficacy endpoint (*mean change in total daily 'ON' Time*)
**Table 2. Summary of secondary efficacy endpoints (ANCOVA LOCF – ITT)**

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th><strong>Safinamide 50–100 mg/day (n=274)</strong></th>
<th><strong>p-value vs placebo (n=275)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS mean treatment difference vs placebo [95% CI]</td>
<td></td>
</tr>
<tr>
<td>ON Time without dyskinesia</td>
<td>0.66 [0.19, 1.12]</td>
<td>0.006</td>
</tr>
<tr>
<td>ON Time with troublesome dyskinesia</td>
<td>0.08 [-0.14, 0.31]</td>
<td>0.463</td>
</tr>
<tr>
<td>OFF Time a</td>
<td>-1.03 [-1.40, -0.67]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPDRS Section III a</td>
<td>-1.82 [-3.01, -0.62]</td>
<td>0.003</td>
</tr>
<tr>
<td>UPDRS Section II a</td>
<td>-0.43 [-1.02, 0.16]</td>
<td>0.149</td>
</tr>
<tr>
<td>CGI-C (mean score at Endpoint) b</td>
<td>-0.44 [-0.62, -0.27]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CGI-C (% patients with improvement) c</td>
<td>57.5% vs 41.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CGI-S a</td>
<td>-0.13 [-0.24, -0.03]</td>
<td>0.012</td>
</tr>
<tr>
<td>PDO-39 Summary Index a</td>
<td>-2.33 [-3.98, -0.68]</td>
<td>0.006</td>
</tr>
<tr>
<td>EQ-5D Index Score a</td>
<td>0.06 [0.03, 0.09]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OFF Time post-morning dose of L-dopa a</td>
<td>-0.18 [-0.28, -0.09]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DRS a</td>
<td>0.23 [-0.14, 0.60]</td>
<td>0.223</td>
</tr>
<tr>
<td>PGIC b</td>
<td>-0.40 [-0.57, -0.22]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GRID-HAMD-17 a</td>
<td>-0.31 [-0.93, 0.30]</td>
<td>0.317</td>
</tr>
</tbody>
</table>
A greater proportion of patients treated with safinamide 50–100 mg compared with those treated with placebo had a statistical significant improvement either when considering the ≥30-minute cut off in both ON and OFF time and a ≥20% improvement in the UPDRS III score, or when considering the ≥60-minute cut off in both ON and OFF time and a ≥30% improvement in UPDRS III scores from baseline to 24 weeks.

The significant benefit of safinamide over placebo in patients with advanced PD observed in the SETTLE study was therefore clinically relevant as it allowed more patients to achieve improvements of at least 1 hour in motor fluctuations and of 30% and more in motor symptoms.
Prescribing

- As an add-on to L-dopa/ DA
- Start at 50mg, can be increased to 100mg
- CI in severe hepatic impairment, no dose reduction for renal impairment
- Avoid co-prescribing with another MAOBI (7 day gap)/Pethidine/retinal problems
- May be used with SSRI at lowest dose (caution)- avoid fluoxetine
Unpublished data - Safinamide

<table>
<thead>
<tr>
<th>n = 47</th>
<th>Average ± St. Dev. (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.2 ± 12 (40-89)</td>
</tr>
<tr>
<td>Sex, ♂</td>
<td>57.4%</td>
</tr>
<tr>
<td>Time of progression/evolution, years</td>
<td>11.4 ± 4 (2-16)</td>
</tr>
<tr>
<td>Hoehn and Yahr, 1, 2, 2.5, 3, 4, 5</td>
<td>0 %, 20 %, 30 %, 48 %, 2 %, 0 %</td>
</tr>
<tr>
<td>L-dopa dose; mg/day</td>
<td>793 ± 216 (400-1300)</td>
</tr>
<tr>
<td>Fluctuations, %</td>
<td>100 %</td>
</tr>
<tr>
<td>Dyskinesias, %</td>
<td>51 %</td>
</tr>
</tbody>
</table>

J. Pagonabarraga, J. Kulisevsky Movement disorders unit, Hospital of Sat Pau Barcelona
Clinical practice

- 100mgs effective for dyskinesia's
- Older people>75, H&Y>3 appear to tolerate drug very poorly
- Significant decrease in off time noted
- In a quarter, L-dopa dose was reduced by 132mg
- Over all well tolerated with good efficacy (57.4% CGI 1 or 2)
Sant Pau Proposed Pathway for Parkinson’s Disease with motor fluctuations

No dyskinesias
- safinamide 50 mg/day
  - Efficacy without development of dyskinesias
    - Maintain safinamide 50 mg/day
  - Efficacy, but development of dyskinesia
    - Increase safinamide 100 mg/day, or lower dose of dopaminergic drugs

Dyskinesias
- safinamide 100 mg/day
  - Efficacy without impairing dyskinesias
    - Increase dose of safinamide 100 mg/day
    - Maintain safinamide 100 mg/day
  - Efficacy with impairing dyskinesias
    - Lower dose of dopaminergic drugs

J. Pagonabarraga, J. Kulisevsky Movement disorders unit, Hospital of Sant Pau Barcelona
Opicapone

Peripheral, selective and reversible COMT inhibitor – Once daily dosing
Well tolerated
Co-administered with L-dopa/DCI
No dose adjustments in older patients
Caution moderate hepatic impairment
Opicapone: clinical experience

- 28 human pharmacology studies are completed
  - more than 900 subjects exposed to OPC
- 2 phase II studies in PD patients are completed
  - more than 40 patients exposed to OPC
- 1 pivotal phase III study in PD patients (BIPARK I, EU) – DB & OL completed
  - 365 subjects exposed to OPC for 14-15 weeks during the double blind phase
  - 495 (92%) entered in OL (of the total completed DB patients)
  - 432 (87%) completed the OL (1-year exposure)
- 1 pivotal phase III study in PD patients (BIPARK II, EU and ROW) – DB & OL completed
  - 275 subjects exposed to OPC for 14-15 weeks during the double blind phase
  - 367 (98%) entered in OL (of the completed DB patients)
  - 286 (78%) completed the OL (1-year exposure)
Opicapone pivotal trials

- **BIA-91067-301 – BIPARK I:**
  - Efficacy and safety of BIA 9-1067 in idiopathic Parkinson’s disease patients with “wearing-off” phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomized, placebo- and active-controlled, parallel-group, multicenter clinical study

- **BIA-91067-302 – BIPARK II:**
  - Efficacy and safety of BIA 9-1067 in idiopathic Parkinson’s disease patients with “wearing-off” phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical study
The investigator freely adjusted the levodopa therapy and/or OPC based on the dopaminergic response and/or associated adverse events.

Doses stable

The investigator freely adjusted the levodopa therapy and/or OPC based on the dopaminergic response and/or associated adverse events.

BIPARK-I and BIPARK II Design

**Double-blind period**

- OPC 5mg
- OPC 25 mg
- OPC 50 mg
- ENT 200 mg
- Placebo

**Open-label extension period**

- OPC 25 mg
- OPC 25 mg (BIPARK-I only) 25 mg or 50 mg according to clinical response

**Visits**

- V1
- V7
- V8
- V9
- V10
- V11
- V12
- V13
- V14

**Days**

- Baseline
- 112±5
- 28±3
- 56±3
- 112±5
- 210±5
- 322±5
- 365±5

**Double-blind period**


# BIPARK: Population characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=121</th>
<th>Entacapone n=122</th>
<th>5 mg OPC n=122</th>
<th>25 mg OPC n=119</th>
<th>50 mg OPC n=116</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y) – mean (SD)</strong></td>
<td>64 (9.3)</td>
<td>64 (8.8)</td>
<td>64 (9.3)</td>
<td>64 (8.9)</td>
<td>64 (9.2)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male – n (%)</td>
<td>71 (58.7%)</td>
<td>76 (62.3%)</td>
<td>71 (58.2%)</td>
<td>67 (56.3%)</td>
<td>69 (60.0%)</td>
</tr>
<tr>
<td>Female – n (%)</td>
<td>50 (41.3%)</td>
<td>46 (37.7%)</td>
<td>51 (41.8%)</td>
<td>52 (43.7%)</td>
<td>46 (40.0%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian – n (%)</td>
<td>121 (100)</td>
<td>122 (100)</td>
<td>122 (100)</td>
<td>119 (100)</td>
<td>115 (100)</td>
</tr>
<tr>
<td><strong>Weight (kg) – Mean (SD)</strong></td>
<td>76 (13.3)</td>
<td>77 (15.0)</td>
<td>75 (12.0)</td>
<td>76 (14.1)</td>
<td>76 (14.5)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²) – mean (SD)</strong></td>
<td>27 (4.3)</td>
<td>27 (4.6)</td>
<td>26 (4.5)</td>
<td>27 (4.3)</td>
<td>27 (4.6)</td>
</tr>
<tr>
<td><strong>Time since:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD diagnosis (y) – mean (SD)</td>
<td>7.7 (4.2)</td>
<td>7.1 (4.1)</td>
<td>7.5 (3.6)</td>
<td>7.2 (4.1)</td>
<td>7.0 (3.8)</td>
</tr>
<tr>
<td>Motor fluctuations (y) – mean (SD)</td>
<td>2.2 (1.9)</td>
<td>2.2 (2.1)</td>
<td>2.3 (2.3)</td>
<td>2.3 (2.5)</td>
<td>2.2 (2.3)</td>
</tr>
<tr>
<td>L-DOPA treatment (y) – mean (SD)</td>
<td>5.8 (3.7)</td>
<td>5.6 (4.1)</td>
<td>5.8 (3.5)</td>
<td>5.9 (3.9)</td>
<td>5.3 (3.8)</td>
</tr>
<tr>
<td>OFF-time (h) – mean (SD)</td>
<td>6.2 (1.8)</td>
<td>6.5 (2.2)</td>
<td>6.7 (2.1)</td>
<td>6.9 (2.2)</td>
<td>6.2 (1.8)</td>
</tr>
<tr>
<td>L-DOPA daily dose (mg) – mean (SD)</td>
<td>675 (302.1)</td>
<td>645 (329.7)</td>
<td>642 (310.3)</td>
<td>654 (324.3)</td>
<td>695 (337.5)</td>
</tr>
</tbody>
</table>

BIPARK I and II
Key primary endpoint- change in absolute OFF-time

**Placebo**
- ENT 200 mg
- OPC 5 mg
- OPC 25 mg
- OPC 50 mg

<table>
<thead>
<tr>
<th>BIPARK-I</th>
<th>LS mean (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.9</td>
</tr>
<tr>
<td>200 mg ENT</td>
<td>-1.6</td>
</tr>
<tr>
<td>5 mg OPC</td>
<td>-1.5</td>
</tr>
<tr>
<td>25 mg OPC</td>
<td>-1.4</td>
</tr>
<tr>
<td>50 mg OPC</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BIPARK-II</th>
<th>LS mean (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-1.1</td>
</tr>
<tr>
<td>25 mg OPC</td>
<td>-1.7</td>
</tr>
<tr>
<td>50 mg OPC</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined</th>
<th>LS mean (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.97</td>
</tr>
<tr>
<td>25 mg OPC</td>
<td>-1.56</td>
</tr>
<tr>
<td>50 mg OPC</td>
<td>-1.94</td>
</tr>
</tbody>
</table>

*P<0.05 vs. placebo
**P<0.0001 vs placebo
*P<0.05 for non-inferiority vs. ENT
BIPARK I and II

Key secondary endpoint - OFF-time responders

OFF-time responder defined as 1 hour or more reduction in absolute OFF-time

- *p<0.05 vs. placebo
- **p<0.0001 vs. placebo

Adapted from: Ferreira J et al. EAN 2015 #P1141; Bial data on file; Ferreira J et al. EAN 2015 #P1142
BIPARK I and II: Secondary endpoint change in ON-time without troublesome dyskinesias

*p<0.05 vs. placebo

Adapted from: Ferreira J et al. EAN 2015#P1141; Lees A et al, MDS 2013 LBA-6; Ferreira J et al. EAN 2015#P1142
# BIPARK: Safety combined analysis

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo n=257</th>
<th>OPC 25 mg n=244</th>
<th>OPC 50 mg n=265</th>
<th>Total OPC n=509</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with a TEAE</td>
<td>147 (57.2%)</td>
<td>152 (62.3%)</td>
<td>170 (64.2%)</td>
<td>322 (63.3%)</td>
</tr>
<tr>
<td>Subjects with a potentially related TEAE</td>
<td>75 (29.2%)</td>
<td>99 (40.6%)</td>
<td>113 (42.6%)</td>
<td>212 (41.7%)</td>
</tr>
<tr>
<td>Subjects with a severe TEAE</td>
<td>16 (6.2%)</td>
<td>10 (4.1%)</td>
<td>17 (6.4%)</td>
<td>27 (5.3%)</td>
</tr>
<tr>
<td>Subjects with a serious TEAE</td>
<td>11 (4.3%)</td>
<td>5 (2.0%)</td>
<td>13 (4.9%)</td>
<td>18 (3.5%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with a TEAE leading to discontinuation</td>
<td>18 (7.0%)</td>
<td>13 (5.3%)</td>
<td>23 (8.7%)</td>
<td>36 (7.1%)</td>
</tr>
</tbody>
</table>
BIPARK: Safety combined analysis

TEAEs occurring with ≥2% in any OPC group vs placebo (safety set)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo</th>
<th>OPC 25 mg</th>
<th>OPC 50 mg</th>
<th>Total OPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Severe n (%)</td>
<td>n (%)</td>
<td>Severe n (%)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>16 (6.2%)</td>
<td>2 (0.8%)</td>
<td>39 (16.0%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (1.9%)</td>
<td>0</td>
<td>12 (4.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (1.6%)</td>
<td>1 (0.4%)</td>
<td>17 (7.0%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (1.2%)</td>
<td>1 (0.4%)</td>
<td>16 (6.6%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Blood CPK increased</td>
<td>5 (1.9%)</td>
<td>1 (0.4%)</td>
<td>7 (2.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (1.2%)</td>
<td>1 (0.4%)</td>
<td>10 (4.1%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (1.9%)</td>
<td>0</td>
<td>10 (4.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (0.8%)</td>
<td>0</td>
<td>4 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0</td>
<td>0</td>
<td>1 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Hallucination</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>6 (2.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Double-blind and open-label extension phases

The investigator freely adjusted the levodopa therapy and/or OPC based on the dopaminergic response and/or associated adverse events.

OPC 5 mg (BIPARK-I only) 25 mg or 50 mg according to clinical response

Visits

<table>
<thead>
<tr>
<th>DB endpoint</th>
<th>V1</th>
<th>V7</th>
<th>V8</th>
<th>V9</th>
<th>V10</th>
<th>V11</th>
<th>V12</th>
<th>V13</th>
<th>V14</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-15 weeks</td>
<td>7±1</td>
<td>28±3</td>
<td>56±3</td>
<td>112±5</td>
<td>210±5</td>
<td>322±5</td>
<td>365±5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OL Extension – Off time change
OL Extension - Off time change
Opicapone- Cardiff Clinical Experience

- 3 patients
- Age group 61-83
- Average duration of Parkinson’s -7.6 years
- On at least 5 daily doses of L-dopa, experiencing wearing off
- 2/3 felt improvement in mobility, speech and ‘madopar lasting longer’
- 1 gent has not experienced any improvement
OTHER DRUGS
PD Psychosis

- Pimavanserin
  - Non-dopaminergic atypical antipsychotic – PD Psychosis and schizophrenia
  - Targets 5HT2a receptors
  - FDA approval to treat hallucinations and delusions associated with psychosis in PD
  - Positive results PII study in AD psychosis
Repurposed drugs

- Exanatide
  - Type 2 Diabetes drug
  - Neuroprotective feature in vitro
  - Results anticipated - UCLH

- Liraglutide/ Victoza
  - Possible role of insulin resistance in neurodegeneration
  - GLP1 receptors
Repurposed Drugs

- **Simvastatin**
  - *Pre-clinical work shows some effect on alpha-synuclein clumping*
  - *Slowing down progression of Parkinson’s*
  - 21 sites across UK (Plymouth)

- **Nilotinimib**
  - *Tyrosine Kinase inhibitor used in CML*
  - *Works by blocking a protein that interfere actions of lysosomes*
  - *Appears to improve symptoms in PD/halt progression*
Other developments

- "Accordion" levodopa pill – “self-peeling capsules”
  - Combined immediate & slow release
  - Unfolds in small intestine over time
  - Twice daily dosing
  - Doses of >1000mg/24 hours required for response
Other developments

- IPX-066 (levodopa controlled release) – Rytary
  - (evidence for 3.6 doses per day vs 5 immediate release)
  - Double total dose needed for same effect
  - Provides more continuous dopaminergic stimulation

- Other levodopa preparations to look out for in future....
  - Nasal inhaled L-dopa
  - Subcutaneous L-dopa
  - SynAgile (Dopafuse) - tooth attached delivery system
Future Trends

- GDNF
  - *Phase 2 trial, Bristol, 41 patients, double blind*
  - *Safe but did not meet primary end point of efficacy*

- Stem Cell transplantation (TRANSEURO)
  - *Evidence form embryonic stem cell, animal models*
  - *Foetal tissue transplants, some promise*
  - *TRANSEURO - ongoing*
Summary

- Newer drugs that address unmet needs of PwP and motor fluctuation/wearing off and dyskinesia's
- Both Safinamide and Opicapone show efficacy – head to head comparator trials
- Limited evidence with older population and frail
- With increased clinical experience and real life data, both Safinamide and Opicapone will occupy key positions in Parkinson’s management algorithm
- Exciting new L-dopa preparations may offer better CDS
- Repurposed drugs may provide future therapy avenues