“Neuroprotection” in Neurodegenerative disorders.
Towards a change in the paradigm?
The mission for this talk is to provide an overview of the recommendations in the new draft guidelines on AD and PD in what concerns “disease modification” claims.
NEUROPROTECTION

HARD: Prevent neurons from dying in a quantitatively meaningful way.
Neuroprotection is a mechanism

**Disease modification is a process.**

However, given the current acceptable semantics, at the level of EMEA guidance we adopted the following concepts:

- **Disease modification** implies that **neuroprotection** is present. There is need to demonstrate the mechanism.

- Delay of disability progression recognizes that an effect that goes beyond the strict control of symptoms happens but does not imply what the mechanism is.
Why are people interested in neuroprotection?

- It is believed that this mechanism will produce *definitive* benefits (long-lasting) while the symptomatic effects are transitory.
  - In real life things are not so clear-cut.
  - It depends on the effect size
    - How many cells will be saved and for how long?
    - It is not reasonable to believe that the degenerative process will be HALTED.

- It will provide the added value that will allow product differentiation and cost justification.
AMYLOID HYPOTHESIS

Parkinson Disease

Alzheimer Disease

ALS

Multiple Sclerosis

IMMUNOLOGIC/INFLAMMATORY
Challenges

- Lack of plausible drug candidates (not so in AD).
- Lack of animal models with good predictive value to establish neuroprotection.
- Disease progression biomarkers are still to be unequivocally established.
- The design and execution of needed trials.
Apoptosis cascade
THE SELECTION OF DRUGS TO PURSUE CLINICAL TRIALS IS FAR FROM BEING OPTIMISED....

“I agree Hepworth you do have drive, ambition and self-confidence, but what we’re looking for is ability.”
The observed progression in both the creatine and minocycline groups did not exceed the predetermined futility threshold. Therefore, the null hypothesis that the means were less than or equal to the threshold value of 7.46 (30% less than the 10.65 DATATOP historical rate of progression) could not be rejected for creatine (p 0.96) or minocycline (p 0.63).

Creatine and minocycline could not be rejected as futile using this analysis and therefore met the criteria for consideration for further clinical testing.

Same results for CQ10 and Gpi 1485
WILL CLINICAL TRIALS EVER CONTRIBUTE TO DISENTANGLE DIFFERENT MECHANISMS (SYMPTOMATIC, DISEASE MODIFICATION)?

UNLIKELY .....
Proposed designs to disentangle symptomatic from disease modifying effects

**Delayed-start design**

*Rasagiline Trial (TEMPO)*

*Withdrawal studies*

*ELLDOPA trial*

**Graphs:**

- Graph showing changes in UPDRS scores over time for different dosage groups.
- Graph showing the change in total score over weeks for various treatment groups and placebo.

*Arch Neurol 2004;61:561*

*NEJM 2004;351:2498*
Interpretation of 2-period trials: main problems

Analysis
- Dropouts
  - Particularly differential dropouts.
- Duration of follow-up/washout.

Results
- A difference at end-point might be due to other effects rather than a "real" DM.
- A difference at end-point might be transitory rather than persistent.

Rather unlikely that any of these trials in presence of a small to medium effect size will be accepted as robust evidence of DM.
Timing of Treatment Initiation in Parkinson’s Disease: A Need for Reappraisal?

Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci, and Jose Obeso, MD, PhD
OBESO-SHAPIRA HYP: Premature speculation or universal Law?

- **BETAFERON in EARLY MS**
- **BENEFIT TRIAL**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with event (up to day 1080)</th>
<th>Risk (Kaplan-Meier estimates up to day 1080)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value (log-rank test)</th>
<th>Absolute risk reduction (day 1080)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDMS</td>
<td>Early treatment (n=292) 99 (34%) Delayed treatment (n=176) 85 (48%)</td>
<td>Early treatment (n=292) 37% Delayed treatment (n=176) 51%</td>
<td>0.59 (0.44-0.80)</td>
<td>0.0011</td>
<td>14%</td>
</tr>
<tr>
<td>McDonald MS</td>
<td>205 (70%) 146 (48%)</td>
<td>74% 85%</td>
<td>0.54 (0.44-0.68)</td>
<td>0.0001</td>
<td>11%</td>
</tr>
<tr>
<td>EDSS progression</td>
<td>Excluding unscheduled visits (main analysis)*</td>
<td>42 (11%) 40 (23%)</td>
<td>16% 24%</td>
<td>0.50 (0.39-0.92)</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Including unscheduled visits*</td>
<td>45 (15%) 42 (24%)</td>
<td>17% 25%</td>
<td>0.51 (0.40-0.93)</td>
<td>0.024</td>
</tr>
<tr>
<td>Unscheduled visits and visits 30 days after relapse excluded*</td>
<td>41 (14%) 38 (22%)</td>
<td>15% 23%</td>
<td>0.51 (0.39-0.95)</td>
<td>0.032</td>
<td>7%</td>
</tr>
<tr>
<td>Unscheduled visits and visits 90 days after relapse excluded*</td>
<td>38 (13%) 36 (20%)</td>
<td>14% 22%</td>
<td>0.50 (0.38-0.95)</td>
<td>0.020</td>
<td>7%</td>
</tr>
<tr>
<td>Unscheduled visits excluded, baseline EDSS as reference?</td>
<td>35 (12%) 37 (21%)</td>
<td>14% 22%</td>
<td>0.54 (0.32-0.91)</td>
<td>0.010</td>
<td>9%</td>
</tr>
<tr>
<td>Unscheduled visits excluded, sustained up to last clinical visit within 3 years*</td>
<td>28 (10%) 27 (12%)</td>
<td>10% 15%</td>
<td>0.51 (0.36-1.03)</td>
<td>0.063</td>
<td>6%</td>
</tr>
</tbody>
</table>
OBESO-SHAPIRA HYP: Premature speculation or universal Law?

3-Year Study of Donepezil Therapy in Alzheimer's Disease: Effects of Early and Continuous Therapy

B. Winblad\textsuperscript{a}, A. Wimo\textsuperscript{b}, K. Engedal\textsuperscript{c}, H. Soininen\textsuperscript{d}, F. Verhey\textsuperscript{e}, G. Waldemar\textsuperscript{f}, A.-L. Wetterholm\textsuperscript{g}, A. Haglund\textsuperscript{g}, R. Zhang\textsuperscript{h}, R. Schindler\textsuperscript{h}, for the Donepezil Nordic Study Group.

\textit{Dementia and Geriatric Cognitive Disorders} 2006;21:353-363

“This study assessed the effects of postponing donepezil treatment for 1 year by comparing patients treated continuously for 3 years with those who received placebo for 1 year followed by open-label donepezil for 2 years. Patients (n = 286) with possible or probable Alzheimer's disease (according to DSM-IV, NINCDS-ADRDA, and Mini-Mental State Examination criteria; see text) were randomized to receive donepezil (5 mg/day for 4 weeks, 10 mg/day thereafter) or placebo (delayed-start group) for 1 year. Of the 192 completers, 157 began a 2-year, open-label phase of donepezil treatment. Outcome measures were the Gottfries-Bråne-Steen scale, the Mini-Mental State Examination, the Global Deterioration Scale, the Progressive Deterioration Scale, the Neuropsychiatric Inventory, and safety (adverse events). Mixed regression analysis was used to compare changes between the groups over 3 years on the efficacy measures. There was a trend for patients receiving continuous therapy to have less global deterioration (Gottfries-Bråne-Steen scale) than those who had delayed treatment (p = 0.056). Small but statistically significant differences between the groups were observed for the secondary measures of cognitive function (Mini-Mental State Examination; p = 0.004) and cognitive and functional abilities (Global Deterioration Scale; p = 0.0231) in favor of continuous donepezil therapy. Over 90% of the patients in both cohorts experienced one treatment-emergent adverse event; most were considered mild or moderate. In conclusion, patients in whom the start of treatment is delayed may demonstrate slightly reduced benefits as compared with those seen in patients starting donepezil therapy early in the course of Alzheimer's disease. These data support the long-term efficacy and safety of donepezil.
Given the low probability that a specific trial design will produce uncontroversial evidence that a product is DISEASE MODYFING, the CHMP considered a 2-step approach leading to new claims.
In 2007 EMEA issue new draft guidelines for PD and AD

- The development of DRUGS is now envisaged in a stepwise process.
- Long-term, parallel design trials that demonstrate the effect of TX in delaying a milestone of disability will be accepted to support a delay of disability claim.
- Trials showing delay of disability + evidence of a change in the pathogenesis through validated biomarkers (yet to be obtained) will support a disease modification claim.
...For regulatory purposes a disease modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition. Consequently a true disease modifying effect cannot be established solely based on clinical outcome data, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme. As this is difficult to achieve without an adequately validated biomarker, a two-step approach may be more suitable. If in a first step delay in the natural course of progression of the disease based on clinical signs and symptoms of the dementing condition can be established, this may be acceptable for a limited claim, e.g. delay of disability. If these results are supported by a convincing package of biological and/or neuroimaging data, e.g. showing delay in the progression of brain atrophy, a full claim for disease modification could be considered.
Some concepts that must be clarified.

- **Validated biomarkers**
  
  **For Diagnosis** – contribute to the increase the likelihood of diagnostic label, which is always probabilistic.

  - It is important to establish its specificity and sensitivity. Its generalisability in normal clinical practice.
  - Issues of relevance: “standard of truth”

  **For Disease Progression**: There is evidence that reflect the behaviour of a relevant disease mechanism and correlates with clinical progression.

- **Surrogate Endpoints**
Surrogate endpoint

- Correlation with the clinical results.
- Changes in the biomarker are reflected in the clinical endpoint.
- The relevance of a difference seen in the biomarkers known in terms of clinical impact.
TO CONCLUDE.....
A change of the research paradigm is warranted...

- To lessen the focus in trying to design mechanistic clinical trials.
- To reinvest in the basics
  - Definition of disease subtypes, eventually based on aetiology.
  - Screening tools for early and pre-symptomatic diagnosis.
  - Cohort studies.
- To analyse treatment effects in an integrated care approach (outcomes research)