Progressive MS Trials: Lessons Learned

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ABSTRACT

Up to very recently, no treatments had proved effective in progressive multiple sclerosis (MS). In 2016, four drugs, two tested in phase 3 and two in phase 2 trials, showed a beneficial effect in primary or secondary progressive MS. Although this could indicate a turning point in progressive MS treatment, most of these successes have been modest and mainly restricted to patients with active inflammation, in the context of trials with powerful anti-inflammatory agents. In April 2017, an International Panel of experts in MS met to discuss the reasons behind the recent successes and past failures in progressive MS trials. This paper summarises these reasons, particularly focusing on the main lessons learned for the design of future trials. First, drugs’ mechanism of action should tackle the specific pathogenic mechanisms that characterise progressive MS. Secondly, trial populations where new drugs are to be tested should be carefully chosen, possibly including younger patients with shorter disease durations, which have greater chances of showing active deterioration during the trial, therefore increasing the power to detect treatment effects. Thirdly, outcome measures used in future phase 2 and phase 3 trials should be highly sensitive and be accompanied by smart trial designs.
INTRODUCTION

Up to very recently, no treatments had proved effective in progressive MS (PMS). In 2016, though, four drugs, two tested in phase 3 trials\textsuperscript{1, 2} and two in phase 2 trials\textsuperscript{3, 4} showed a beneficial effect in PPMS or SPMS. This change in direction has prompted the revision of the reasons underlying recent chain of successes and past failures.

In this paper, we aim to focus on those reasons behind past failures and recent successes. First, we will focus on the drugs tested in past PMS trials, most of them not specifically designed to tackle the pathogenic mechanisms that characterise the PMS phenotype. Second, we will discuss the type of patient included in PMS trials, which has probably had an enormous influence over the observed results. Finally, we will mention some methodological issues of these trials, mainly related to outcome measures and trial designs, that could have played a role in past failures as well as in recent achievements.

DRUGS IN PROGRESSIVE MS TRIALS

Many of the drugs that have been tested in PMS trials were not initially designed to tackle the specific pathogenic mechanisms that characterise the PMS phenotype. Instead, they tended to be the same as those tested in RRMS trials (Tables 1 and 2). This could be justified by the fact that all pathological traits in MS are thought to coexist throughout the disease, as part of a continuum, being the differences between stages or phenotypes more quantitative than qualitative\textsuperscript{5, 6}. However, these differences, even if relatively small, may have played a part in the negative results found so far in PMS trials. In addition, the rationale for some of the phase 3 trials carried out in PMS was provided by the results of phase 2 studies performed in RRMS\textsuperscript{7-9} (not in PMS) or by the post-hoc subgroup analyses of PMS trials which had
overall had negative results\textsuperscript{10-12}. Therefore, the non-optimal choice of the drug might have been aggravated by the performance of large phase 3 trials without a previous phase 2 trial in progressive MS with the same drug, which could have helped to save time and economic resources.

However, not all drugs tested in PMS have failed to show a beneficial effect in delaying disability progression. In 1998, the European Study Group on interferon beta (IFN)-1b in SPMS published the results of the first phase 3 trial in SPMS\textsuperscript{9} (i.e. the EUSPMS trial), and these were positive for the primary endpoint (\textbf{Table 1}). Additionally, mitoxantrone, a powerful anti-inflammatory treatment, also showed a beneficial effect in a phase 3 trial with SPMS patients, published in 2002\textsuperscript{13}. Unfortunately, though, despite these initially promising results, the use of IFNb or mitoxantrone in PMS has been progressively reduced in the clinic, for different reasons. With regard to IFNb, the initial positive results could not be confirmed by the rest of the phase 3 trials also carried out with IFNb in SPMS\textsuperscript{14-16} or PPMS\textsuperscript{17, 18}. This was attributed to EUSPMS trial population being younger and with higher inflammatory activity, i.e. more similar to the RRMS phenotype, than other trial populations\textsuperscript{19}. This implied a loss of confidence in the use of IFNb for SPMS, for which it had been approved in some countries, especially in those patients without any clear evidence of acute macroscopic inflammation, visible with T2-weighted MRI sequences. In relation to mitoxantrone, it is its poor safety profile\textsuperscript{20} that has limited its use, which is nowadays almost anecdotal in western countries.

In 2014, the scenario of treatments for MS started to change when the results of the phase 2 MS-STAT trial, which evaluated the efficacy of high doses of simvastatin versus placebo in SPMS, were published\textsuperscript{4}. Simvastatin showed an ability to reduce the rate of brain volume loss, the primary outcome, and to delay the
progression of disability\textsuperscript{4,21}. Remarkably, unlike the IFNb and the mitoxantrone trials, the choice of the drug in the MS-STAT trial was based on a careful evaluation of its possible neuroprotective effects\textsuperscript{22}.

In 2016, the results of the phase 3 ORATORIO trial were published\textsuperscript{1}, meaning the major breakthrough in PMS treatment. The ORATORIO trial showed a clear superiority of ocrelizumab, an anti-CD20 monoclonal antibody, as compared to placebo, in delaying the accrual of disability in patients with PPMS. Remarkably, it was the first time that a drug showed efficacy in PPMS\textsuperscript{1}. In this case, although no evidence from any phase 2 trials of ocrelizumab in PMS was available before the start of the trial, several studies had already shown a potential role of CD20 B-cells in the pathogenesis of progressive MS\textsuperscript{23-25}. B-cells accumulate in the subarachnoid space of patients with PMS, in the so-called meningeal follicles\textsuperscript{23-25}, and this constituted the main rationale for the ORATORIO trial. Additionally, a post-hoc subgroup analysis of the OLYMPUS trial (published in 2009) had shown some beneficial effect of rituximab, another anti-CD20 monoclonal antibody similar to ocrelizumab, in younger PPMS patients with inflammatory activity\textsuperscript{26}. So, although the OLYMPUS trial had been deemed overall negative, the results of this subgroup analysis also contributed to the rationale for the use of ocrelizumab in the ORATORIO trial.

The biotin trial for PMS, also published in 2016, showed as well significant results in the primary endpoint\textsuperscript{3}. As happened in the ORATORIO trial, the rationale for the use of biotin was not its efficacy in RRMS, but its unique mechanism of action: biotin activates carboxylases which enhance either the synthesis of fatty acids, therefore supporting myelin repair, or the energy production in neurons, therefore protecting against hypoxia-driven axonal degeneration\textsuperscript{27}. 
Finally, the phase 3 EXPAND trial of siponimod in SPMS, presented at ECTRIMS 2016, has also shown a beneficial effect versus placebo\textsuperscript{2}, contributing to the list of recent trials successful in PMS. Here, although the drug had proved effective in a phase 2 RRMS trial (BOLD study) and had a clear anti-inflammatory effect\textsuperscript{28}, it also seemed to have neuroprotective effects within the CNS after crossing the blood-brain barrier\textsuperscript{29}. This latter characteristic constituted the main rationale for its use in SPMS\textsuperscript{4}.

Thus, it seems that with all these recent successes, a new era of PMS trials might have started. However, a few considerations need to be made. First, unfortunately, a careful selection of the drug has not always meant obtaining significant results. A clear example is the phase 3 INFORMS trial with fingolimod, a drug with a similar profile to that of siponimod, which failed to show efficacy in PPMS\textsuperscript{8}. Second, since most of the successful drugs in PMS also had a clear direct anti-inflammatory effect, it could be argued that this was in fact the main responsible for their success, rather than their neuroprotective effect. In fact, even in those trials with positive results, the benefits have been modest and have been predominantly restricted to patients with active inflammation, indicating that effective therapies positively impacting the pathophysiology of later stages of progressive MS are still elusive. Therefore, more research into the pathogenic mechanisms of PMS and the mechanisms of action of the potential drugs for PMS is still needed.

**TRIAL POPULATIONS**

The choice of the trial population is crucial to be able to capture treatment effects, should they exist. There are at least two potential causes of an eventual unfortunate choice of trial population: first, the lack of an appropriate definition of progressive
MS; second, the ignoring of patients’ disease severity when defining the inclusion criteria.

In relation to the definition problem, in 1996, Lublin and Reingold published the first definitions of MS phenotypes\textsuperscript{30}. These could be homogeneously used across the scientific community and meant a significant improvement in trial design\textsuperscript{30}. However, the lack of precision of the definitions of SPMS and PPMS, which could not easily incorporate the presence of clinical or MRI activity, prompted the publication of the new definitions of the progressive forms of MS, in 2014\textsuperscript{6}. These allowed us to use MS disease modifiers to specify whether the patient had clinical/MRI inflammatory activity or active progression, on top of the diagnosis of SPMS or PPMS, which could be very useful for future trial selection.

The problem related to ignoring patients’ severity in the inclusion criteria has started to be tackled more recently. A trial population with slower disease progression than that considered when estimating the required sample size may not be powered to detect differences between groups, should they exist. For instance, when in 2007 the phase 3 PROMISE trial was published\textsuperscript{31}, one of the reasons attributed to its negative results was the low progression rate in the placebo arm, which was not predicted when designing the trial. A strategy used to avoid unexpected low rates of progression of disability has been the inclusion of patients with greater chances of having an active disease over the course of the trial. This was the strategy of the ORATORIO trial\textsuperscript{1}. In this study, one of the inclusion criteria was to have a relatively short disease duration, especially if the patient was not too disabled. This ensured that only patients with steeper accrual of disability were included. However, high progression rates have also been seen in negative studies, such as the INFORMS trial, where the proportion of patients with progression in the
placebo arm was 70%\(^8\). This suggests that other factors apart from the presence of high progression rates may have also been involved in the success of the ORATORIO trial. In fact, in the ORATORIO trial, an additional inclusion criteria was that patients had to be 55 years old or younger, whereas previous studies had allowed the inclusion of patients with ages up to 65\(^3\). So, this younger trial population ensured the participation of patients with greater inflammatory activity\(^1\), more likely to respond to anti-inflammatory treatment regimes. Of note, although the ORATORIO trial did not show any statistical differences between subgroups defined by inflammatory activity, this was attributed to the lack of power\(^1\). Thus, it may be possible that the success in the ORATORIO trial was more strongly related to the presence of a population with a more inflammatory phenotype\(^1\), possibly as a consequence of choosing younger participants, than to the presence of high progression rates, although both may have contributed.

In general, these trials where the study populations are carefully selected to increase their power are considered ‘enriched’ trials. Importantly, despite the advantages of enriched trials, they may also entail some drawbacks, such as questioning the generalisability of the results to all PMS patients, with and without the trial population features. An alternative to enriched trials may be the performance of subgroup analyses within the trial population to assess whether the efficacy of a drug is similar in different subpopulations. Subgroup analyses are generally performed if previously defined in the trial protocol. In that case, the trial is usually adequately powered for that. Nevertheless, if there is a scientific rationale, it is not inappropriate to conduct a subgroup analysis that was not previously defined in the trial protocol. Thus, it may be reasonable to approach these post-hoc analyses as exploratory and recognise their limited power.
OUTCOME MEASURES AND TRIAL DESIGNS

Phase 3 trials in PMS have clinical measures as primary endpoints. Among these, the EDSS-related measures are the most widely used (see Tables 1 and 2). However, the EDSS has limitations\textsuperscript{32-34}, which may well have been responsible for the lack of significant results in PMS trials.

Over the years, phase 3 trials in progressive MS have tried different strategies to overcome the limitations of the EDSS. One of these was to substitute the EDSS by another clinical score with a greater sensitivity to clinical progression, such as the Multiple Sclerosis Functional Composite (MSFC) score\textsuperscript{33}, which reflects better than the EDSS the upper limb and cognitive functions. For instance, the IMPACT study, which in 2002 showed a beneficial effect of IFNb-1a in SPMS when compared to placebo, had used the changes in MSFC scores during the trial as primary endpoint.

Another strategy to overcome the limitations of the EDSS has consisted of using composite outcomes of clinical progression instead of a single score. For example the MIMS (mitoxantrone, SPMS)\textsuperscript{13}, the CUPID (dronabinol, SPMS)\textsuperscript{35}, the ASCEND (natalizumab, SPMS)\textsuperscript{36} and the INFORMS (fingolimod, PPMS)\textsuperscript{8} trials used composite measures of clinical progression, always involving the EDSS. Nevertheless, despite the use of composite primary endpoints, only the MIMS study\textsuperscript{13} of all these was significant. Also following this strategy, in the ORATORIO study, the composite NEP (no evidence of progression) was used as an exploratory secondary endpoint\textsuperscript{1}, emulating the commonly used NECA (no evidence of clinical activity) and NEDA (no evidence of disease activity) for RRMS trials\textsuperscript{37-40}. In the
ORATORIO study, significant treatment effects were not only seen in the primary endpoint, but also in the NEP endpoint: the proportion of patients without progression in the EDSS, NHPT and TWT (all three) was higher among those receiving ocrelizumab than in the placebo arm. A final strategy has resided in changing completely the focus of the outcome measure from clinical progression to clinical improvement. Although ‘percentage of patients with clinical improvement’ had been already used as secondary endpoint in a few RRMS trials such as the phase 3 Copolymer-1 and CARE-MS II, it was used as primary endpoint for the first time in the biotin trial for progressive MS (Table 1). Of note, although the use of improvement of disability (instead of delayed progression) as trial primary endpoint is still debatable, it is possible that it reflects a genuine aspect of some drugs for progressive MS. This would be especially true for drugs with a neuroprotective or restorative mechanism of action, as was the case for biotin.

Phase 2 trial endpoints mainly consist of non-clinical outcome measures. In progressive MS, the most widely used is the brain atrophy rate, which in the MS-STAT trial was the responsible for the differences between treatment groups in favour of simvastatin. On the other hand, its responsiveness is still limited and great efforts are being made to develop new phase 2 outcome measures able to detect treatment effects in 6-12 months, instead of the conventional 24 months (Tables 1 and 2). Along these lines, the recently completed SPRINT-MS trial, apart from aiming at the comparison of ibudilast versus placebo to delay the disability accumulation in SPMS and PPMS, aimed at head-to-head comparisons of several imaging measures in terms of their ability to reflect treatment effects.

Regarding the trial design, the vast majority of the PMS trials –and of the MS trials in general– so far have used the classic 1:1 scheme, where one active arm is
compared to one placebo arm. And in those few trials with two active arms compared to one placebo arm\textsuperscript{13, 16, 17, 46}, the two active arms tested two doses of the same drug, rather than two active components (Tables \textbf{1} and \textbf{2}). Recent evidence from Oncology trials suggests that this trial design could be improved by comparing several active drugs to the placebo arm\textsuperscript{47}. Following this innovative multi-arm trial suggestion, the phase 2 MS-SMART study was born. It aimed to compare three active drugs, fluoxetine, amiloride and riluzole, to placebo, in a proof-of-concept drug-repurposing four-arm placebo-controlled trial, which finished the recruitment in June 2016 and is currently ongoing\textsuperscript{48}.

\textbf{CONCLUSIONS}

The recent chain of successes in SPMS and PPMS trials has brought some light to the bleak prospect we used to have in relation to treatment options for PMS. So far, one of these newly tested drugs, the ocrelizumab, has already been approved for patients with PPMS\textsuperscript{49} and it is likely that more drugs are approved in the near future. Thus, this set of fortunate concatenated events might be meaning a turning point in the history of trials for PMS, enabling us to assess the reasons behind past failures and latest achievements. On the other hand, most of these successes have been modest, mainly restricted to patients with active inflammation and in the context of trials with powerful anti-inflammatory agents. Thus, although inflammation in progressive MS exists and the presence of meningeal follicles is a well-known pathogenic mechanism, there are other processes beyond inflammation that have not been successfully addressed by many of the drugs recently tested. Therefore, it is not surprising that a number of significant failures have also occurred over the previous years, despite a careful choice of the tested drug.
In sum, it has become clearer that drugs’ mechanism of action must tackle the specific pathogenic mechanisms that characterise progressive MS in order to increase the chances of success. Also, the trial populations where new drugs are to be tested should be carefully chosen. Younger populations with shorter disease durations and more rapid progression rates have greater chances of showing active deterioration during the years of the trial, therefore increasing the power to detect treatment effects, should these exist. Finally, outcome measures in both phase 2 and phase 3 trials should be as sensitive as possible to detect treatment effects within a short time frame, and be accompanied by a smart trial design able to maximise the potential of the trial to find effective drugs in a quick and efficient manner.
REFERENCES

32. Noseworthy JH, Vandervoort MK, Wong CJ and Ebers GC. Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems
49. Food and Drug Administration FDA and US Department of Health and Human Services US. 
   2017.
**Table 1. Main trials in SPMS**

<table>
<thead>
<tr>
<th>Drug tested (vs. placebo)</th>
<th>Trial</th>
<th>Condition (no. of patients randomised)</th>
<th>Duration</th>
<th>Primary endpoint(s)</th>
<th>Results on the primary endpoint</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN beta-1b SC 8 million IU eod</td>
<td>Phase 3 (EUSPMS study) (^1)</td>
<td>SPMS (n=718)</td>
<td>Early termination due to obvious superiority of IFN (initially planned: 39 months)</td>
<td>Time to 3-month CDP on the EDSS (^2)</td>
<td>Positive</td>
<td>European Study Group on IFN beta-1b in SPMS, Lancet 1998, phase 3</td>
</tr>
<tr>
<td>IFN beta-1a SC 22µg or 44µg thrice weekly</td>
<td>Phase 3 (SPECTRIMS study) (^1)</td>
<td>SPMS (n=618)</td>
<td>36 months</td>
<td>Time to 3-month CDP on the EDSS (^2)</td>
<td>Negative</td>
<td>Li et al. (SPECTRIMS Study Group), Neurology 2001</td>
</tr>
<tr>
<td>IFNb-1b SC 250µg or 160µg/m(^2) of body surface area eod</td>
<td>Phase 3 (NASPMS study) (^1)</td>
<td>SPMS (n=939)</td>
<td>Early termination for futility (initially planned: 36 months)</td>
<td>Time to 6-month CDP on the EDSS (^2)</td>
<td>Negative</td>
<td>Panitch et al. (North American Study Group on IFN beta-1b in SPMS), Neurology 2004</td>
</tr>
<tr>
<td>IFN beta-1a IM 60mcg/week</td>
<td>Phase 3 (IMPACT study) (^1)</td>
<td>SPMS (n=436)</td>
<td>24 months</td>
<td>Change in the MSFC from baseline to 24 months</td>
<td>Positive</td>
<td>Cohen et al., Neurology 2002</td>
</tr>
<tr>
<td>IFN beta-1a SC 22mcg/week</td>
<td>Phase 3 (The Nordic SPMS study) (^1)</td>
<td>SPMS (n=371)</td>
<td>36 months</td>
<td>Time to 6-month CDP on the EDSS (^2)</td>
<td>Negative</td>
<td>Andersen et al., JNNP 2004</td>
</tr>
<tr>
<td>Mitoxantrone IV 12 mg/m(^2) or 5 mg/m(^2) of body surface area/3 months</td>
<td>Phase 3 (MIMS study)</td>
<td>SPMS or PRMS course (n=188)</td>
<td>24 months</td>
<td>Multivariate analysis of five clinical measures: -EDSS changes (baseline-final); -AI changes (baseline-final); -No. of treated relapses; -Time to first treated relapse; -Change in standardised neurological status;</td>
<td>Positive</td>
<td>Hartung et al., Lancet 2002</td>
</tr>
<tr>
<td>Treatment</td>
<td>Phase</td>
<td>Study</td>
<td>Patient Count</td>
<td>Time</td>
<td>Primary Endpoint</td>
<td>Result</td>
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<tr>
<td>IVIG 1g/Kg/month</td>
<td>Phase 3</td>
<td>(ESIMS study)²</td>
<td>SPMS (n=318)</td>
<td>24 months</td>
<td>Time to 3-month CDP on the EDSS²</td>
<td>Negative</td>
</tr>
<tr>
<td>MBP8298 IV 500mg/6 months</td>
<td>Phase 2</td>
<td>SPMS (n=32)</td>
<td></td>
<td>24 months</td>
<td>Change in the EDSS from baseline to 24 months</td>
<td>Negative</td>
</tr>
<tr>
<td>MBP8298 IV 500mg/6 months</td>
<td>Phase 3</td>
<td>(MAESTRO study)³</td>
<td>SPMS (n=612)</td>
<td>24 months</td>
<td>Time to 6-month CDP on the EDSS²</td>
<td>Negative</td>
</tr>
<tr>
<td>Lamotrigine PO 400mg/day</td>
<td>Phase 2</td>
<td>SPMS (n=120)</td>
<td></td>
<td>24 months</td>
<td>Rate of change of partial (central) cerebral volume over 24 months</td>
<td>Negative</td>
</tr>
<tr>
<td>Dronabinol PO (max. dose: 28mg/day, titrated against bodyweight)</td>
<td>Phase unspecified</td>
<td>(CUPID study)</td>
<td>SPMS (n=302), PPMS (n=191)</td>
<td>36 months</td>
<td>-Time to 6-month CDP on the EDSS² -Change in the MSIS-29-PHYS from baseline to 36 months</td>
<td>Negative</td>
</tr>
<tr>
<td>Simvastatin PO 80mg/day</td>
<td>Phase 2</td>
<td>SPMS (n=140)</td>
<td></td>
<td>24 months</td>
<td>Annualised rate of whole-brain atrophy</td>
<td><strong>Positive</strong></td>
</tr>
<tr>
<td>Natalizumab IV 300mg/4 weeks</td>
<td>Phase 3</td>
<td>(ASCEND study)</td>
<td>SPMS (n=887)</td>
<td>24 months</td>
<td>Composite outcome: 6-month CDP on EDSS², or TWT (≥20%), or NHPT (≥20%)</td>
<td>Negative</td>
</tr>
<tr>
<td>Biotin PO 100mg/8h</td>
<td>Phase 2</td>
<td>Progressive MS: SPMS (n=99) or PPMS (n=55)</td>
<td></td>
<td>12 months</td>
<td>Proportion of patients with improvement of MS-related disability⁶ at month 9, confirmed at month 12</td>
<td><strong>Positive</strong></td>
</tr>
<tr>
<td>Siponimod PO 2mg/day</td>
<td>Phase 3</td>
<td>(EXPAND study)</td>
<td>SPMS (n=1105)</td>
<td>37 months</td>
<td>Time to 3-month CDP on the EDSS²</td>
<td><strong>Positive</strong></td>
</tr>
</tbody>
</table>

**Table 1** (footnote).
1: The rationale for the phase 3 trials with IFNb in SPMS was provided by the results of trials carried out in RRMS; 2: The definition of EDSS progression depends on the baseline EDSS score; 3: The rationale for the ESIMS trial was provided by the results of uncontrolled studies and placebo-controlled trials in RRMS; 4: Although the results for the main analysis were negative, in the subgroup of 20 patients with HLA haplotypes DR2 and/or DR4, MBP8298 treatment had a significant effect on the primary endpoint; 5: The rationale for the MAESTRO study was provided by the results of the subgroup analysis with HLA haplotypes DR2 and/or DR4; 6: Improvement was defined as: decrease of ≥0.5 point or ≥1 point in EDSS (if baseline score was 6–7 or 4.5–5.5, respectively) or a ≥20% decrease in timed walk test (TWT) time, compared with the best EDSS or TWT value recorded at either the screening or the randomisation visit.

Abbreviations: AI: ambulation index; EDSS: expanded disability status scale; CDP: confirmed disability progression; IFNb-1a/1b: interferon beta 1a/1b; IV: intravenous; MSFC: multiple sclerosis functional composite; MSIS-29-PHYS: physical impact subscale of the 29-item multiple sclerosis impact scale; NHPT: nine-hole peg test; PO: per oral; PPMS: primary progressive multiple sclerosis; PRMS: progressive-relapsing MS; RRMS: relapsing-remitting MS; SC: subcutaneous; SPMS: secondary progressive MS; TWT: timed walk test;
Table 2. Main trials in PPMS

<table>
<thead>
<tr>
<th>Drug tested (vs. placebo)</th>
<th>Condition (no. of patients randomised)</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Results on the primary endpoint</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA SC 15mg/12h</td>
<td>Phase 2</td>
<td>Chronic progressive MS (n=106); out of these, 31 had PPMS (n=23) or ‘transitional progressive MS’ (n=8)</td>
<td>24 months</td>
<td>Time to confirmed progression on the EDSS</td>
<td>Negative²</td>
</tr>
<tr>
<td>GA SC 20mg/day</td>
<td>Phase 3 (PROMiSe study)</td>
<td>PPMS (n=943)</td>
<td>Early termination for futility (initially planned: 36 months)</td>
<td>Time to 3-month CDP on the EDSS</td>
<td>Negative</td>
</tr>
<tr>
<td>IFNb-1a IM 30µg or 60µg weekly</td>
<td>Phase 2</td>
<td>PPMS (n=50)</td>
<td>24 months</td>
<td>Time to 3-month CDP on the EDSS</td>
<td>Negative</td>
</tr>
<tr>
<td>IFNb-1b SC 8 MIU eod</td>
<td>Phase 2</td>
<td>PPMS and ‘transitional progressive MS’ (n=73)</td>
<td>24 months</td>
<td>Time to 3-month CDP on the EDSS</td>
<td>Negative</td>
</tr>
<tr>
<td>Rituximab IV 1000mg/24 weeks</td>
<td>Phase 2/3 (OLYMPUS study)</td>
<td>PPMS (n=439)</td>
<td>96 weeks</td>
<td>Time to 3-month CDP on the EDSS</td>
<td>Negative³</td>
</tr>
<tr>
<td>Fingolimod PO 0.5mg/day</td>
<td>Phase 3 (INFORMS study)³</td>
<td>PPMS (n=970)</td>
<td>36 months</td>
<td>Composite endpoint: Time to 3-month CDP on either EDSS, or TWT, or NHPT</td>
<td>Negative</td>
</tr>
<tr>
<td>Ocrelizumab IV 600mg (300mg x2) /24 weeks</td>
<td>Phase 3 (ORATORIO study)³</td>
<td>PPMS (n=732)</td>
<td>120 weeks</td>
<td>Percentage of patients with 3-month CDP on the EDSS</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Table 2 (footnote).

1: The definition of EDSS progression depends on the baseline EDSS score; 2: In the subset of 31 patients with either PPMS or transitional progressive MS, some hint of efficacy was observed; this motivated the phase 3 trial; 3: In the subgroup of 72 patients with age <51 years and presence of gadolinium-enhancing lesions in the MRI, rituximab significantly delayed progression of disability (vs. placebo); 4: The rationale for the INFORMS trial was provided by in-vitro and in-vivo studies that suggested that fingolimod could inhibit neurodegeneration. No phase 2 trial was performed with fingolimod in PPMS; 5: The rationale for the ORATORIO trial was provided by the results of the subgroup analysis of the OLYMPUS trial (in younger patients with inflammatory activity). No phase 2 trial was performed with ocrelizumab in PPMS; 6: Although the primary endpoint was the percentage of patients with CDP, this percentage was obtained through a time-to-event analysis.

Abbreviations: EDSS: expanded disability status scale; CDP: confirmed disability progression; IFNb-1a/1b: interferon beta 1a/1b; IV: intravenous; NHPT: nine-hole peg test; PO: per oral; PPMS: primary progressive multiple sclerosis.