**Additional file 7: Overview of methods used to differentiate symptomatic from disease-modifying effects of putative disease-modifying agents in all included randomised controlled trials in Alzheimer’s disease**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Wash-in analysis** | **Wash-out analysis** | **Delayed-start trial design** | **Long-term follow-up** | **Biomarkers (primary or secondary outcome measures)** | | | | | **Time-to-event outcomes** |
| **Imaging** | **CSF** | **Blood** | **Urine** | **EEG** |
| Aβ immunisation [1] |  |  |  | 15 months¥ | Volumetric MRI | Aβ  Total tau |  |  |  |  |
| LEADe [2] |  | 8 weeks |  | 18 months† | Volumetric MRI |  |  |  |  |  |
| Bapineuzumab (phase 3) APOE ε4 carriers [3] |  |  |  | 18 months† | PiB PET  Volumetric MRI | Phospho-tau |  |  |  |  |
| Bapineuzumab (phase 3) APOE ε4 non-carriers [3] |  |  |  | 18 months† | PiB PET  Volumetric MRI | Phospho-tau |  |  |  |  |
| Bapineuzumab (phase 2) [4] |  |  |  | 18 months† | Volumetric MRI | Aβ42  Phospho-tau  Total tau |  |  |  |  |
| ABBY [5, 6] |  |  |  | 17 monthsФ | Volumetric MRI | Unspecified |  |  |  |  |
| BLAZE [6-8] |  |  |  | 17 monthsФ | AV-45 PET  FDG PET  Volumetric MRI | Unspecified |  |  |  |  |
| Scyllo-inositol [9] |  |  |  | 18 months† | MRS Volumetric MRI | Aβ40, Aβ42  Phospho-tau  Total tau |  |  |  |  |
| IDENTITY [10, 11] |  | 16 weeks | 18 month delay |  | AV-35 PET  FDG PET Volumetric MRI | Aβ42  Phospho-tau  Tau | Aβ |  |  |  |
| IDENTITY2 [12] |  | 16 weeks | 18 month delay |  | AV-35 PET  FDG PET Volumetric MRI | Aβ42  Phospho-tau  Total tau | Aβ |  |  |  |
| Simvastatin [13] |  |  |  |  |  | Aβ40, Aβ42 |  |  |  |  |
| EXPEDITION 1 [14] |  |  |  | 18 months† | AV-45  Volumetric MRI | Aβ40, Aβ42  Phospho-tau  Total tau | Aβ40  Aβ42 |  |  |  |
| EXPEDITION 2 [14] |  |  |  | 18 months† | AV-45  Volumetric MRI | Aβ40, Aβ42  Phospho-tau  Total tau | Aβ40  Aβ42 |  |  |  |
| Tarenflurbil (phase 3) [15] |  |  |  | 18 months‡ |  |  |  |  |  |  |
| Tarenflurbil (phase 2) [16] |  |  | 12 month delay | 24 months† |  |  |  |  |  |  |
| **Trial** | **Wash-in analysis** | **Wash-out analysis** | **Delayed-start trial design** | **Long-term follow-up** | **Biomarkers (primary or secondary outcome measures)** | | | | | **Time-to-event outcomes** |
| **Imaging** | **CSF** | **Blood** | **Urine** | **EEG** |
| Alphase [17] |  |  |  |  | Volumetric MRI | Aβ and tau | Aβ | Aβ |  |  |
| DARAD [18] |  |  |  | 12 months† |  |  |  |  |  |  |
| T-817MA [19] |  |  |  | 12 monthsФ | Volumetric MRI |  |  |  |  |  |
| Celecoxib [20] |  |  |  | 12 months¥ |  |  |  |  |  |  |
| DAD2000 [21] |  |  |  | 12 monthsФ |  |  |  |  |  |  |
| Diclofenac + misoprostol [22] |  |  |  | 6 months¥ |  |  |  |  |  |  |
| Docosahexaenoic acid [23] |  |  |  | 18 months† | Volumetric MRI |  |  |  |  |  |
| OmegAD [24] |  |  | 6 month delay | 12 months† |  |  |  |  |  |  |
| Escitalopram [25] |  |  |  |  | Volumetric MRI |  |  |  |  |  |
| Hydroxychloroquine [26] |  |  |  | 18 months† |  |  |  |  |  |  |
| Ibuprofen [27] |  |  |  | 12 months¥ |  |  |  |  |  |  |
| Dutch indomethacin [28] |  |  |  | 12 months¥ |  |  |  |  |  |  |
| American indomethacin [29] |  |  |  | 6 months¥ |  |  |  |  |  |  |
| Masitinib (phase 2) [30] |  |  |  | 6 months† |  |  |  |  |  |  |
| Prednisone [31] |  |  |  | 12 months¥ |  |  |  |  |  |  |
| Resveratrol [32] |  |  |  |  | Volumetric MRI | Aβ40, Aβ42  Phospho-tau  Total tau | Aβ40 Aβ42 |  |  |  |
| Rofecoxib [33] |  | 12 weeks |  | 12 months† |  |  |  |  |  |  |
| Rofecoxib or naproxen [34] |  | 8 weeks |  |  |  |  |  |  |  | Time to the following separate endpoints: (1) 4 point decline in ADAS-cog; (2) 1 step worsening on global CDR; (3) 15 point decline on ADCS-ADL; (4) institutionalisation; (5)death |
| DAV.I.D.E .[35] |  |  | 12 month delay | 24 months† |  |  |  |  |  |  |
| Nutritional formulation [36] |  |  | 3-6 month delay |  |  |  |  |  |  |  |
| Czech/Slovak selegiline [37] | 6 and 12 weeks |  |  | 6 months¥ |  |  |  |  | Dominant frequencies |  |
| Canadian selegiline [38] |  | 12 weeks |  |  |  |  |  |  |  |  |
| KUOSTAD [39] |  |  |  | 36 monthsФ |  |  |  |  |  |  |
| Nebraska selegiline [40] |  |  |  | 15 months¥ |  |  |  |  |  |  |
| Selegiline & tocopherol [41] |  |  |  | 24 months† |  |  |  |  |  | Time to either severe dementia (Global CDR = 3), loss of ability to perform basic ADLs, institutionalisation, or death |
| **Trial** | **Wash-in analysis** | **Wash-out analysis** | **Delayed-start trial design** | **Long-term follow-up** | **Biomarkers (primary or secondary outcome measures)** | | | | | **Time-to-event outcomes** |
| **Imaging** | **CSF** | **Blood** | **Urine** | **EEG** |
| VALID [42] |  | 8 weeks |  | 24 months† | Volumetric MRI |  |  |  |  | Time to clinically significant agitation or psychosis (defined as a score of ≥ 3 on ≥ 1 NPI items assessing delusions, hallucinations and agitation/aggression) |
| TauRx (phase 2) [43] |  |  |  | 6 months† | HMPAO SPECT |  |  |  |  |  |
| Donepezil MRI/MRS [44] |  | 6 weeks |  | 6 months† | MRS  Volumetric MRI |  |  |  |  |  |
| Donepezil international [45] |  | 6 weeks |  | 6 months† |  |  |  |  |  |  |
| Donepezil USA clinical [46] |  | 6 weeks |  | 6 months† |  |  |  |  |  |  |
| Galantamine [47] | 12 weeks |  | 6 month delay | 12 months† |  |  |  |  |  |  |
| GAP Study [48, 49] |  |  |  | 18 monthsФ | AV-45 PET  FDG PET | Aβ42  Phospho-tau  Total tau |  |  |  |  |
| CONCERT [50, 51] |  |  |  | 12 monthsФ |  |  |  |  |  |  |
| CONNECTION [52, 53] |  |  |  | 6 monthsФ |  |  |  |  |  |  |
| Russian Dimebon [54] |  |  |  | 6 months† |  |  |  |  |  |  |
| Cerebrolysin [55] | 4 weeks | 12 weeks |  | 6 months† |  |  |  |  |  |  |
| Memantine PET [56] |  |  |  |  | FDG PET | Aβ40, Aβ42  Phospho-tau  Total tau |  |  |  |  |
| Memantine MRI [57] |  |  |  |  | Volumetric MRI |  |  |  |  |  |
| Memantine MRS [58] |  |  |  |  | MRS |  |  |  |  |  |
| Memantine vs. donepezil MRS [59] |  |  |  |  | MRS |  |  |  |  |  |
| Memantine multimodal [60] |  |  |  |  | FDG PET  MRS  Volumetric MRI |  |  |  |  |  |
| REFLECT-1 [61] |  |  |  | 6 months¥ |  |  |  |  |  |  |
| Rosiglitazone genetics [62] |  |  |  | 6 months† |  |  |  |  |  |  |
| Azeliragon [63] |  |  |  | 18 months† | Volumetric MRI | Aβ1-x  Aβ40, Aβ42  Phospho-tau  Total tau |  |  |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Wash-in analysis** | **Wash-out analysis** | **Delayed-start trial design** | **Long-term follow-up** | **Biomarkers (primary or secondary outcome measures)** | | | | | **Time-to-event outcomes** |
| **Imaging** | **CSF** | **Blood** | **Urine** | **EEG** |
| **Planned, Ongoing and**  **Unpublished RCTs** |  |  |  |  |  |  |  |  |  |  |
| Pfizer Bapineuzumab  APOE ε4 carriers [64] |  |  |  | 18 months | Volumetric MRI  PiB PET | Phospho-tau |  |  |  |  |
| Pfizer Bapineuzumab  APOE ε4 non-carriers [65] |  |  |  | 18 months | Volumetric MRI  PiB PET | Phospho-tau |  |  |  |  |
| Carvedilol [66] |  |  |  | 6 months |  | Aβ |  |  |  |  |
| Marguerite RoAD [67] |  |  |  | 24 months | AV-45 PET  Volumetric MRI | Aβ  Phospho-tau  Total tau |  |  |  |  |
| GENISTEÍNA\_2 [68] |  |  |  |  |  | Aβ  Phospho-tau |  |  |  |  |
| NILVAD [69] |  |  |  | 18 months |  |  |  |  |  |  |
| NIC5-15 [70] |  |  |  | 6 months |  |  | Aβ |  |  |  |
| PIT-ROAD [71] |  |  |  | 12 months |  |  |  |  |  |  |
| EXPEDITION 3 [72] |  |  | 18 months  (extension study) | 18 months | AV-45 PET  Volumetric MRI | Aβ | Aβ |  |  |  |
| CLASP [73] |  |  |  | 18 months |  |  |  |  |  |  |
| Global efficacy tarenflurbil [74] |  |  |  | 18 months |  |  |  |  |  |  |
| European 3APS [75] |  |  |  | 18 months |  |  |  |  |  |  |
| EPOCH [76] |  |  | 18 months  (extension study) | 18 months | Volumetric MRI  Vizamyl PET | Phospho-tau  Total tau |  |  |  |  |
| Masitinib (phase 3) [77] |  |  |  | 6 months |  |  |  |  |  |  |
| SUN-AK [78] |  |  |  | 18 months | Volumetric MRI |  |  |  |  | Time to the following endpoints: (1) hospitalisation; (2) death related to Alzheimer’s disease |
| MNEMOSYNE [79] |  |  |  | 6 months |  |  |  |  |  |  |
| Rasagiline Rescue [80] |  |  |  |  | FDG PET |  |  |  |  |  |
| RGM [81] |  |  |  | 12 months |  |  |  |  |  |  |
| AD-IDEA [82] |  |  |  | 6 months |  |  |  |  |  |  |
| TRx-237-005 [83] |  |  |  | 18 months | FDG PET  Volumetric MRI | Unspecified |  |  |  |  |
| **Trial** | **Wash-in analysis** | **Wash-out analysis** | **Delayed-start trial design** | **Long-term follow-up** | **Biomarkers (primary or secondary outcome measures)** | | | | | **Time-to-event outcomes** |
| **Imaging** | **CSF** | **Blood** | **Urine** | **EEG** |
| TRx-237-015 [84] |  |  |  | 15 months | FDG PET Volumetric MRI | Unspecified |  |  |  |  |
| AMBAR [85] |  |  |  | 14 months | FDG PET  Volumetric MRI | Aβ40, Aβ42  Phospho-tau  Total tau | Aβ40  Aβ42 |  |  |  |
| NOURISH AD [86] |  |  |  | 6 months |  |  |  |  |  |  |
| Riluzole [87] |  |  |  |  | MRS  FDG PET |  |  |  |  |  |
| STEADFAST [88] |  |  |  | 18 months | FDG PET Volumetric MRI |  | Aβ |  |  |  |

**Key**

**Long-term follow-up studies (published studies only)**

**Biomarker modalities** † Image published (e.g. Kaplan Meier plot) from which the presence/absence of sustained

CSF Cerebrospinal fluiddivergence in outcome measures could be inferred. No formal slope analyses conducted.

EEG Electroencephalography ‡ Formal slope analyses conducted to look for sustained divergence.

MRI Magnetic Resonance Imaging ¥ No formal slope analysis conducted nor image published from which sustained divergence

MRS Magnetic Resonance Spectroscopy in outcome measures between groups can be inferred. Furthermore, no alternative

PET Positron Emission Tomography strategy used to try to demonstrate disease-modification.

SPECT Single Photon Emission Computed Tomography Ф Insufficient information to classify (e.g. only published as conference abstract)

**Proteins Clinical rating scales**

Aβ Amyloid beta ADAS-cog Alzheimer’s Disease Assessment Scale – cognitive subscale [89]

Aβ40 Amyloid beta isomer, length 40 amino acids ADCS-ADL Alzheimer’s Disease Cooperative Study – Activities of Daily Living inventory [90]

Aβ42 Amyloid beta isomer, length 42 amino acids Global CDR The Washington University Clinical Dementia Rating global score [91]

NPI Neuropsychiatric Inventory [92]

**PET ligands**

AV-45 (E)-4-(2-(6-(2-(2-(2-18F-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methyl benzenamine

FDG [18F]-2-fluoro-2-deoxyglucose

PiB [11C]Pittsburgh compound B

Vizamyl [18F]-flutemetamol

**SPECT ligands**

HMPAO [99mTc]-hexamethylpropylene amine oxidase

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