Screening rounds

R1

Jan 01 2013- Jan 01 2020

Sept 20

Alzheimer disease OR Alzheimer's disease OR AD OR Parkinson disease OR Parkinson's disease OR PD OR ALS OR Amyotrophic lateral sclerosis OR Huntington disease OR Huntington's disease

R2

Sept 26-Jan 01 2013- Jan 01 2020

MS (Multiple Sclerosis) OR MS OR Migraine OR Headache OR Epilepsy OR TBI OR Traumatic Brain Injury OR Stroke

R3

Sept 28

1. 01/01/2011-12/31/2012

Alzheimer disease OR Alzheimer's disease OR AD OR Parkinson disease OR Parkinson's disease OR PD OR ALS OR Amyotrophic lateral sclerosis OR Huntington disease OR Huntington's disease OR

MS (Multiple Sclerosis) OR MS OR Migraine OR Headache

1. 01/01/2011-12/31/2012

Epilepsy OR TBI OR Traumatic Brain Injury OR Stroke

1. 01/02/2020-01/01/2021

Alzheimer disease OR Alzheimer's disease OR AD OR Parkinson disease OR Parkinson's disease OR PD OR ALS OR Amyotrophic lateral sclerosis OR Huntington disease OR Huntington's disease OR MS (Multiple Sclerosis) OR MS OR Migraine OR Headache

<https://clinicaltrials.gov/ct2/download_studies?cond=Alzheimer+disease+OR+Alzheimer%27s+disease+OR+AD+OR+Parkinson+disease+OR+Parkinson%27s+disease+OR+PD+OR+ALS+OR+Amyotrophic+lateral+sclerosis+OR+Huntington+disease+OR+Huntington%27s+disease+OR+MS+%28Multiple+Sclerosis%29+OR+MS+OR+Migraine+OR+Headache&term=&type=Intr&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=01%2F02%2F2020&prcd_e=01%2F01%2F2021&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=>

01/02/2020-01/01/2021

Epilepsy OR TBI OR Traumatic Brain Injury OR Stroke

<https://clinicaltrials.gov/ct2/download_studies?cond=Epilepsy+OR+TBI+OR+Traumatic+Brain+Injury+OR+Stroke&term=&type=Intr&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=01%2F02%2F2020&prcd_e=01%2F01%2F2021&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=>

degen additional including the ones that were excluded from R1 that were excluded but should be included from new rules

R4

Extra (got lost)

R5

MS expanded terms just added Multiple Sclerosis

R6

Trials with Limited data

R7

P2/3 trials that needed to be reincluded, MS trials that we found pubs for later, ones with no results

Add 1s in round 7 column and ones that need pubs from MS category and p3s that pass the P3 test

Lons answers about symptoms

|  |  |  |
| --- | --- | --- |
| **Indication:** | **Symptom** | **Used as a measure of disease modification? (yes/no)** |
| **AD** | Insomnia | No |
| Apathy | No |
| Agitation | No |
| Sleepiness | No |
| **Huntington’s** | Chorea | DK - possibly |
| **Stroke** | Fatigue | No |
| Walking deficits | No |
| **MS** | Chronic Visual Loss Related to Optic Neuritis | DK posibly |
| Processing speed | DK – doubt it |
| Pain | No |
| **PD** | Sleepiness | No |
| Apathy | No |
| **TBI** | Mood disorders | No |
| Affect Recognition | No |
| Sleepiness | No |
| **Migraine** | Dizziness | Not in itself |

**Erika**

|  |  |  |
| --- | --- | --- |
| **Indication:** | **Symptom** | **Used as a measure of disease modification? (yes/no)** |
| Huntington’s | Chorea | Yes |
| Optical neuritis | No |
| Cognition | Yes |
| Stroke | Verbal fluency | Possibly |
| Epilepsy | Postictal Central Respiratory Dysfunction | No |

**excludes**

* + - Stroke-verbal fluency in manual
    - MS-optical Neuritis in includes

1. We’ve come across some phase 3 trials in MS that use weird endpoints. Would you consider any of the following “widely used measures of disease modification of MS” for phase 3 trials? (I am pretty sure the answer is ‘no’ but want to double check)
2. All make sense as primary-maybe not as primary endpoint
   1. fatigue-rarely
   2. walking-as secondary endpoint yes. It's called T25W
   3. spasticity-rarely
   4. processing speed-as tertiary endpoint
   5. chronic visual loss related to optic neuritis-Vision is part of the EDSS, so yes very often. some trials focused on vision. Then they used retinal fiber thicknes by OCT.
   6. cognitive disorders-in some as secondary or tertiary endpoint
   7. cognition-same
3. Athough all these endpoints are most often used in trials on secondary or primary progressive forms of the disease. In RRMS, primary endpoint is mostly annualised relapse rate

**Allowed symptom treatments**

**Huntington’s-chorea and cognition**

PD-motor function

General function scores

TASKS TO DO

* Me
  + Phase check
    - (phase 2 or phase 3 check in matching doc— b/c of ss need to check avg enrollment for that p3 indication in that indication
    - p2/3s are included as long as they don’t say they didn’t continue?)
  + Check for new formulation/new modalities
    - Matching
  + Combo
    - Finish my check-monotherapy
    - Check the author email-send the drafts after figure it out (accidentally sent one
  + Data finalize
    - Last matching questions
    - Consort
  + After Data finalized
    - If anything moved from exclude to include check approval and positivity (ms emails symptoms)
    - SMD check
    - when data finalized see if other indications can go into SMD?
* Karine
  + Check for new formulation/new
    - Includes
    - Matching
  + combo stuff
  + New publications

SEVERITY Checks- take it out

Qualitatively- severe disease may play a roll in

Severe

substantial reduction of years of life lived or severe disability

DMT-

A disease-modifying treatment is a pharmacologic or other intervention that affects the underlying neurobiology of the disease (neuroprotective)

Conditions

|  |  |  |  |
| --- | --- | --- | --- |
|  | Severe | DMT SOC | Severely morbid  Severe + no DMT |
| Alzheimer's disease | Yes | No2 | Yes |
| Parkinson disease | Yes | No3 | Yes |
| Amyotrophic lateral sclerosis | Yes | Yes-Riluzole4 | yes |
| Huntington's disease | Yes | No5 | Yes |
| Relapsing Multiple Sclerosis | No | Yes | No |
| Progressive Multiple Sclerosis |  |  |  |
| Primary | Yes | No | Yes |
| Secondary | - | Yes6 | yes |
| Headache | No | Yes | No |
| Epilepsy |  |  |  |
| TSC-associated Refractory Seizures | No | No7 | No |
| Partial Onset Seizure | No | No7 | No |
| Dravet Syndrome | Yes | No7 | Yes |
| Lennox-Gastaut Syndrome | Yes | No7 | Yes |
| TBI | No | - | No |
| Stroke | Yes | No | Yes |

Urgent treatment need-PD, AD, HD, PPMS, Lennox-Gastaut Syndrome, Dravet Syndrome, Stroke

No-Headache, RMS, SPMS, ALS, Partial Onset Seizure, TSC-associated Refractory Seizures, TBI

Combo adjuvant stuff

If already preceded-wont matter

Ambigious-would matter

Bypass would matter

1st check

If matched on adjuvant status-was marked as earlier evidence is ok

If didn’t match on adjuvant status-now considered a match

If p3 is adjuvant and p2 is mono

If p3 is mono and p2 is adjuvant

Combos still needed combo prior evidence, but monotherapy evidence could be used for adjuvant P3s because it may just be a result of shifting populations from early line to late line patients. Adjuvant trials were identified by the terms “adjuvant” or “add on”. Adjuvant evidence could not be used for monotherapy P3s

Mono to Adjuvant –early to late

Adjuvant to mono—late to early

Would need to search for earlier p3 bc mono P3 would now be excluded if adjuvant P3 and adjuvant P3 would now be excluded if mono p3. And check all P3 trial matches that are not preceeded

Added to soc compared to soc ?

**New version of old drug check**

Want to exclude because drugs that are SLIGHT variations on old drugs-either because they have made a small molecular change or changed the delivery mechanism because these trials have a heightened level of evidence available from trials on the original drug. This is akin to earlier P3 evidence.

Whole criteria is reliant on citations-cant check everything same family of drug does not count

* 1. Read the introductions for all of our trials and mark if this is the case and what the earlier drug is.
     1. Cite evidence of drugs with similar names-mention changing delivery mechanism or molecular make up of existing drug
  2. The earlier drug should have reached P3 or approval status in this indication
     1. If this is true-exclude
     2. If it didn’t reach P3 or approval, this evidence can be used as P2 evidence

1. Need to check all P2 matches for diff versions of the same initial drug as earlier p3 evidence?

**Combo check**

1. **First, put each trial into the following three categories**
   1. **Monotherapy**
   2. **Adjuvant**
      1. **Call it an adjuvant, add-on**
      2. **typically new+SOC**
   3. **True combo** 
      1. **they are interested in how the drugs work together**
      2. **could be SOC+SOC**
      3. **could be new+new**
2. **Reconcile- Next, we need to redo search for earlier P3 and P2 evidence** 
   1. **Monotherapy** 
      1. **Has this treatment been investigated as a adjuvant first?** 
         1. **Does it cite adjuvant evidence-this should now count as earlier p3 or p2**
         2. **Trialviewer too**
   2. **Adjuvant** 
      1. **Has this treatment been investigated as a monotherapy first?** 
         1. **Does it cite monotherapy evidence-this should now count as earlier p3 or p2**
         2. **Trialviewer too**
   3. **True combo** 
      1. **don’t need to worry-only combo evidence can count-already did this**
3. **Bring matches to matching doc and update and exclude those that had prior P3 evidence**