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
  + When waiting on JK
    - Clean matching
      * phase 2 or phase 3 check in matching doc— b/c of ss filter for the ones relying on ss --need to check avg enrollment for that p3 indication in that indication
      * Check biomarker unsures
      * Sodium lactate
    - check code
* Karine
  + 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

**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**

**Discussion**

In addition, initiating a P3 trial without positive clinical or validated surrogate evidence from a P2 trial likely diminishes its likelihood of being positive. `

Ambigious is imprt bc getting lots of information from trial outside of clinical positive result-still learning something

MS -overproving efficacy in MS in P2 shouldn’t be running P3, what are the implications for bypass-maybe its good we should do it

Don’t call the preceded group positivity on clinical endpoint-need to say positive on a positive clinical or validated surrogate endpoint.

Explain why headache is weird for wdae

Nonpositive likely included subgroup analyses that were positive that gave them a different reason to believe in positivity. However these are notoriously x and reviews often advice against this.

Cannot make much conclusions on

Limitations

P2/3s are put into preceded category although unsure if P2 had a clinical positive endpoint-different threshold to move to P3

Some phase2s found sig safety concerns and were terminated but we didn’t capture this

P2/3s letting them be evidence for themselves but don’t really know if they proceeded-especially ones without papers

p2/3s are included as long as they don’t say they didn’t continue or call it a P2 in the publication

sometimes cant find pubs or results that trialst might have used. These trials are put into the true bypass group.

sometimes no clear primary

only p3 trials that are the first in the indication.

Sometimes p2 had no accessible results- in these cases we called it true bypass because how could it be used to influence p3 trial. But may be same sponsor and hogged the informations.

Some indications may have no clinical or validated surrogate endpoint available (PMS)

Future research

How much of bypass group are made up from modifications of existing approved drugs?

Citation analysis

Further research should evaluate whether bypassing is more prevalent in indications more desperate for treatment like AD vs. MS and migraine. There may be a difference in the rate of bypass between disease types because speed may have a different amount of influence on drug development in areas with established standards of care.

Not all repourposing drugs

MS does not bypass much and is more likely to be positive- is this the bypass or is that a product of ms drug development

We gave them so much leeway- dose, population, treatment could be diff formulation or diff adjuvant status. The ones that bypass truly bypassed evidence about that treatment in every sense of the word

Limitation-why is walking diff than optical neuritis

<https://journals.lww.com/neurotodayonline/fulltext/2015/09030/NEWS_FROM_THE_ALZHEIMER_S_ASSOCIATION.6.aspx?casa_token=G8S79pHqaqoAAAAA:ZawunakDBKnA91wcmvnFELAa0-ivjuPMSbcrrzOk2Bz-e7NBtLOi0vT6-2HMRBzV0V8n0Se54Sa8iimNRz8YDCOuZ53F>

data shows that the real issue is not the cases where they ran a p2 trial not aimed at efficacy-but rather the cases where they start a p2 trial off of neg results-maybe driving the results. Doesn’t seem clear that the lack of optimizing the intervention ensemble is the reason for the effect. Potentially what this is showing us is that P2 trials may be most usufel as a go/no go step to stop investigating

.Maybe we need long trials looking at “medically meaningful” results such as clinical or validated surrogate measures.3 Alternatively, proof of concept P2 trials may be enough to start a P3 trial without sacrificing efficacy.15 This desire for speed should without putting large numbers of patients and money into futile trials.

except that headaches themselves may be a risk, and the drug works on headaches. so if drugs are highkly effective, then that might explain ur resulys

EXTRA

Each P3 trial was categorized depending on the level of evidence available from P2 trials prior to its initiation. This to further understand whether P3 trial success is impacted by the presence of information on the intervention ensemble or on clinical efficacy.

Hail mary

without putting large numbers of patients and money into futile trials.

Therefore, bypassing P2 trials and the information gained from them may impact the future of the drug development trajectory.

In addition, trials in Alzheimer’s disease have been called a “necessary step in drug development.”18

. without putting large numbers of patients and money into futile trials.

the presence of P2 positive efficacy evidence from a P2 trial, the pure presence of a P2 trial and the opportunity to optimize the intervention ensemble, or whether P2 trial results did not impact P3 trial results

**Identification**

Trial records identified from ClinicalTrials.gov (n = 1188)

**Records excluded semi-automatically (n=647):**

• Without an “actual” primary completion date (n=142)

• Non-randomized (n=216)

• Small sample size (n=83)

Trial Status is withdrawn (n=1)

• Primary purpose is diagnostic, screening, or basic science (n=3)

• Incorrect intervention or indication (n=80)

• No US/CAD/EU/Australian enrollment site (n=119)

• Duplicates (n=3)

**Screening**

Studies manually assessed for eligibility (n =541)

**Studies excluded manually (n=428):**

• Intervention did not match our criteria (n=51)

• Comparator did not match our criteria (n=17)

• Indication did not match our criteria (n=146)

• No primary efficacy endpoint (n=49)

• Not the first P3 trial in drug/indication pair (n=159)

• Phase 2/3 that did not continue to P3 portion (n=6)

Phase 3 Trials included in review (n=113)

**Included**

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**A screenshot of a computer

Description automatically generated with low confidence**

**Chart

Description automatically generated******