Supplement

P3 Sample Creation

CT.gov SEARCH PARAMETERS For Phase 3 Trials:

1. Condition or disease: Alzheimer disease OR Alzheimer's disease OR Alzheimer Dementias OR Dementia of the Alzheimer's type OR dementia alzheimers OR Dementia of Alzheimers Type OR dats OR Alzheimer Type Dementia OR Senile Dementia OR Alzheimer Syndrome OR AD OR Parkinson disease OR Parkinson's disease OR PD OR Parkinson OR Primary Parkinsonism OR Paralysis Agitans OR Shaking palsy OR ALS OR Amyotrophic lateral sclerosis OR Gehrig Disease OR Motor neurone disease OR Charcot disease OR Huntington disease OR Huntington's disease OR Huntington's chorea OR Chronic progressive hereditary chorea OR MS OR Multiple Sclerosis OR MS (Multiple Sclerosis) OR Disseminated sclerosis OR Migraine OR Cephalalgia OR Head pain OR Pain in head OR Cephalgia OR Headache OR Epilepsy OR epileptics OR seizure disorders OR epilepsia OR TBI OR Traumatic Brain Injury OR brain traumas OR Traumatic encephalopathy OR brain injuries traumatic OR traumatic brain damage OR Brain damage OR cerebral damage OR injury brain OR cerebral injury OR Stroke OR Cerebrovascular accident OR cerebral vascular accident OR Apoplexy OR Brain attack OR Brain Vascular Accident
2. Study type: “Interventional Studies (Clinical Trials)”
3. Status of recruitment: no restriction (looking for Actual primary completion dates, so likely mostly Completed/Terminated/Active not recruiting but completed- checked filtered results to see)
4. Phase: 3
5. Study start date: no restriction
6. Primary completion date: 01/01/2011-01/01/2021

The end range was chosen to allow one year between primary completion and depositing results as per the Final Rule.1 Our objective was to have at least 100 phase 3 trials but we saturated the sample for a full decade of Phase 3 trials. The target minimal sample size of 100 is selected because, for a primarily descriptive study, it seems likely to deliver a reasonably robust estimate of the prevalence of phase 3 bypass. Assuming 30% trials involve phase 2 bypass, availability of 30 trials involving bypass provides a reasonable starting point for secondary objectives for a first ever exploration of the prevalence of bypass.

SEMI-AUTOMATIC SCREENING (using excel filters) For Phase 3 Trials:

1. Primary completion date: checked that type is “Actual” and not “Anticipated”
   1. Excluded, \*unless\* trial had an “Actual” overall completion date;
2. Trial design: excluded if trial was labelled as:
   1. “Non-randomized” in randomization field;
   2. “Single group assignment” in “Model” field;
   3. 1 in “Arms” field;
3. Trial size: <30
4. Trial status: exclude if the trial recruitment status was:
   1. Withdrawn (i.e. no patients enrolled);
5. Indication: excluded if primary purpose is
   1. Diagnostic;
   2. Screening;
   3. Basic Science
6. Intervention/Treatment: excluded if trial:
   1. Did not include at least one intervention that was classified as a “Drug” or “Biological” “ Dietary supplement” or “genetic” (“Other” and “combination product” is manually checked); ie exclude procedure or behavioral or device or radiation
   2. Included healthy volunteers;
7. Trial Location: exclude if the trial does not have a
   1. US or CAD UK, EU, Australian

MANUAL SCREENING For Phase 3 Trials:

1. Intervention: Exclude if the intervention is
   1. surgery/behavioral/device/conditioning of stem cells
   2. extension, discontinuation studies
   3. head to head (trials pitting two SOC interventions against each other) or if there are more than two options for the experimental arm (ake “any anticoagulant)
   4. treating a second condition in our conditions (ie infection in PD patients) (immune responses to vaccines)
   5. biosimilar against what it is biosimilar to (new formulations or type of administration are included)
2. Comparator
   1. must use a comparator that is either placebo or another treatment (as opposed to another dose of same drug (Although it can be a change in the delivery mechanism), no historical controls)
3. Indication-Must investigate treatment for the below conditions exclusively:
   1. Alzheimer's disease, Parkinson disease, Amyotrophic lateral sclerosis, Huntington's disease, Multiple sclerosis (RRMS, PPMS, SPMS), Headaches, Epilepsy, TBI and Stroke recurrence.
4. First Phase 3 trial: Must be the first phase 3 trial for the treatment/indication pair registered on clinicaltrials.gov (unless there are phase 3 trials that are started within a year of each other and not completed) (or cited by the publication). We used TrialViewer to search for all earlier phase 3 trials of our experimental drug-of-interest. We used the following rules for determining if earlier phase 3 trials counted as evidence for the trial in our sample.
   1. If the intervention is a change in the administration of a different drug, P3 trials investigating the other drug are not counted as prior evidence
   2. If the intervention is treating a symptom of a condition
      1. If there are prior trials investigating the same treatment in the same condition treating the same symptom, or has outcomes looking at the general condition,-these can be used as prior evidence
      2. If there are prior trials investigating a different symptom in the same condition and does not look at general condition modification or the symptom in our trial-this is not prior evidence.
   3. Prior trials that investigate treatments in preclinical populations are not used as prior evidence
      1. Exp: CIS or people with AD mutation
   4. To count as a prior P3 evidence for trials in our sample, earlier trials
      1. did not need to be exclusively in that indication
      2. could be Phase 4 or 3
      3. the same intervention could be in control or exp arm, just needed to have been studied in a phase 3 trial in that indication before
      4. Trials investigating could treatment in children could be evidence for adults and other way around
      5. Same Day year before is earlier evidence
   5. When the trial in our sample is labeled adjunctive, only trials labeled adjunctive or in combination with the same drugs will be counted as prior evidence
   6. RRMS and Progressive MS were treated separately, they could not be used as prior evidence for the other. If the trial was only SPMS, it could cite either RRMS or PMS.
   7. Headaches are broken into types (Migraines and other headache types could not be used as prior evidence for the other.
   8. we did not check for the status of the previous trial.
5. Trials were included if they had a primary endpoint that was a clinical efficacy endpoint (including trials looking at a symptom used as measure of disease modification)
   * + 1. Trials were excluded if they only had primary safety, tolerability or surrogate primary endpoints or primary endpoints looking only at a symptom that is not used as a measure of disease modification (pseudo-symptoms)
6. Phase 2/3 trials that did not progress to the P3 portion were excluded
   * + 1. In one case, a phase 2/3 trial in our sample noted that it did not progress to a phase 3 and instead moved to a new phase 3 nct number. We included the new nct number because the earlier evidence was explicitly noted in the publication to be a phase 2 trial not a phase 3?????
7. No phase 3 results
   * + 1. The Google Scholar search used NCT ID, Title (top-line & official), varying combinations of drug names, indication, and sponsor & investigator last name. The OVID search using MEDLINE and EMBASE used a combination of the search terms: drug names from the experimental arm (any synonym of the drug mentioned in ClinicalTrials.gov should be included), and indication as listed in ClinicalTrials.gov , and “Clinical trial”, and “Phase 3”.
       2. Primary results are defined as reporting the results on at least one primary outcome with a significance test performed.
       3. If this did not turn up primary publications of results:
          1. We will use primary Ct.gov results. If there are no primary ct.gov results:

We will use abstracts reporting primary results. If none are available:

We will use abstracts reporting interim results but only if the trial was terminated

Trials without results are included in the primary but not in the positivity analysis

That are not terminated and did not have primary results

That are terminated and did not have interim results

**Phase determination:** We use how it is defined on ct.gov in the phase category unless they call themselves something else in the publication or the ct.gov record. If still not defined, we used the following rules.

* P1-Not controlled and no efficacy endpoint
* P2-- Call itself dose-ranging, or proof of concept, All that does not fall into the other two categories (Can be controlled or not controlled, can have an efficacy endpoint, and has a small\* number of patients)
* P3- Controlled and have primary efficacy endpoints and large\* number of patients

\*Dependent on indication: for now: 300

Matching P2 trials to P3 trials

P2/3 are put into the proceeded category automatically. If the P2 trial was terminated with no data or an extension study, it is not counted as prior evidence. Otherwise, to determine if a P2 trial was eligible to be a match, it had to have a primary start date that is a year or more earlier than primary start date of the phase 3 study in our sample, as indicated by ClinicalTrials.gov (or the recruitment start date of the publication if registration date was unavailable). If the date that the P2 trial started is unclear, publication within/before the year that the P3 trial started is accepted. Expanded access trials, trials without any results were not applicable. In addition, P2 trials had to also match on:

1. Indication
   1. Phase 2 trials were only considered a match to the phase 3 trial in our sample if it is in the same condition. To ensure our approach for matching phase 2 and 3 trials was standardized and reproducible, we allowed any P2 trial in the same BROAD disease area count as an earlier phase 2 trial for the phase 3 trials in our sample.**)** Our broad disease areas are Alzheimer’s disease, Parkinson’s disease, ALS, Huntington’s disease, Multiple sclerosis\*, Migraine, Headache, Epilepsy, TBI and Stroke recurrence.

\*Relapse Remitting MS and Progressive MS were treated separately, and they could not cite the other as prior evidence. If the trial was only SPMS, it could cite either RRMS or PMS.

1. Intervention
   1. P2 trials had to investigate the same drug or biologic
      1. A trial that investigates a drug/biologic as a monotherapy cannot be used as prior evidence for a trial that is investigating the same drug in combination therapy (and vice-versa)
      2. If the one trial is x+any drug in a category (choleresterase inhibitors) and the other is x+one drug of that type-this is used as prior evidence
      3. If there was a change in the formulation of the drug, the old formulation did not count as prior evidence

Positivity of P2 matches

We used the definition of positivity provided by the trial including using sequential testing procedures regardless of whether they modified their primaries. When there were two primary analyses where one was positive and the other was not (inconsistent results), we used the following rules:

1. Co-primaries: When they stated that all primaries had to be positive for the trial to be positive, we called inconsistent results nonpositive. When they don’t change the sig level
2. Multiple primaries: In this case, each primary endpoint is tested at a significant level determined by the method for multiplicity adjustment or simply by the partition of the alpha levels. we called inconsistent results positive\*if; they call it coprimaries but adjust the primary as is common with multiple primaries we will treat as multiple
3. In cases where there were 2 dose groups are both considered primary analysis groups, we called inconsistent results positive

Classification

Each P3 trial was classified into one of the following groups based on its prior evidence:

* + To be put into the preceded group
    - P2 trial that had a clinical primary endpoint that was positive as defined in the trial
    - P2 trial that had an approved primary surrogate endpoint that was positive as defined in the trial. Surrogate endpoint will only be included in this group if
      * They are reasonably validated “biomarkers of disease pathophysiology”2 type 2 biomarkers3 This was also discussed with a neurologist. No AD surrogates were accepted.
        + 2They are commonly used in phase 2 trials in that indication because of time constraints and makes sense mechanistically and have been validated in a P3 trial of a similar drug showing clinical efficacy is associated with it
        + Allowed

MS-Number of lesions

MS-responder rate, defined as the proportion of patients with ⩾95% peripheral CD19+ B-cell depletion from baseline within 2weeks

PD- levodopa PK levels

* + To be put into the ambiguous group: every other trial with a matched P2 trial
    - Had a P2 trial that was nonpositive on their primary clinical efficacy endpoint, had a P2 trial that had a primary endpoint investigating surrogate endpoints (not approved), or investigating safety/tolerability etc.
  + To be put in the bypass group
    - No matched P2 trial
* If any p3 trial had more than one prior trial, the one closest to preceded will take priority

Extraction

* Termination status
  + And whether it was due to futility or safety concerns. This was found on registration records or in publications
  + There were two that were terminated at interim and guessed it was futility—why we cant separate futility and safety for termination
* Positivity status
  + All P3 trials in our sample had to have a primary clinical endpoint. They were deemed to be positive if they were positive on a primary outcome
    - We looked at p-values and the definition of positivity in the statistical analysis section to determine trial positivity. If there was no definition of positivity, Trials with multiple primary outcomes were considered positive if one of them was positive.
  + Otherwise, trials were deemed to be non-positive.
* When available, we extracted SMD of efficacy endpoints and the withdrawals due to AEs
  + When there were different dose groups as the primary
    - Took the one that is first for hierarchical testing. If there truly was not one higher priority we took the higher dose. If one was added as an amendment, the original was taken.
  + SMDs
    - For AD trials, where multiple SMDs were often available, ADAS cog was taken (if available)
    - Only taken when it was a primary
    - Took the most adjusted p-value available.
    - AD: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog)
      * Variations of ADAS-cog (11, 12, 13, 14, 15) will be meta-analyzed using the standardized mean difference (SMD)
    - PD: Unified Parkinson's Disease Rating Scale (UPDRS)
      * UPDRS total scores (from subscales I-III or I-IV) extracted if available. Otherwise, combined UPDRS II+III or UPDRS III scores were extracted. UPDRS “off” scores (measurements recorded while dopaminergic therapies are not affecting patient symptoms) were extracted in trials of patients experiencing motor fluctuations where UPDRS data was reported in both the “on” and “off” states. UPRS data will be meta-analyzed with SMD.
  + WdueAE
    - From ct.gov or consort documents in the publications. Where there was disagreement, the publication took priority. We tried to make this the same group as was taken for SMD but if it was not possible could be different (broader groups)
    - Took from baseline randomization as denominator (earliest that was available
* Approval status
  + Trials were classified as pre/post approval for the treatment under investigation at the time of trial initiation (primary start date in registration)
    - Pre-approval = drug was approved after the primary start date or never approved  
      post-approval = drug was approved before the primary start date
  + Approval did not need to be in the same indication or delivery mechanism
  + In combination, if both are approved separately we call post approval
  + If the trial is looking at a new formulation for an old drug- the first formulation will be used for approval date
* Funding (industry vs nonindustry).
  + If no funder was available, we took the sponsor
  + Any industry involvement was classified as industry-funded
    - What to do about when it was not pharma but the drug was supplied by pharma

Protocol Deviations

* Did not search pubmed
* Positivity of p2 was not include times when there are multiple trials with conflicting results,
* Did not look at these variable
  + Phase 2/3 vs P2 (these were all preceded)
  + Pediatric vs Adult vs Mixed (all were adult)
  + Orphan disease (all were not orphan (except maybe HD)
  + Symptom (most were excluded)
* Did not do d (separated into true bypass and ambiguous bypass
* In addition, we will estimate the proportion of patients in our sample that were in P3 trials that bypassed.
* Moral econ-did not use neg used nonpositive
  + Did all trials not Within the five disease areas with the largest number of trials in our sample,
  + Did not do In addition, we will estimate the proportion of patients in our sample that were in P3 trials that bypassed.
* SMD and Wdae analyses needed 3 in each group with SMD numbers available