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.21 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
   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)
   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 and PMS), Migraine, Headache, 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). 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 b be evidence 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
5. Trials without a primary efficacy endpoint were excluded
6. treating a symptom of our condition that is not used as a measure of disease modification (pseudo-symptoms)
7. Phase 2/3 trials that did not progress to the P3 portion were excluded

Search for P3 publications

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”.

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. 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 (RRMS & PMS separately), Migraine, Headache, Epilepsy, TBI and Stroke recurrence.
2. 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

To be deemed **positive**, P2 trials must have a primary clinical efficacy endpoint and be positive on that endpoint based on what was pre-specified in the trial. If positivity was not defined in the publication and there were two groups investigated where one was positive and the other was not, we marked these as positive because they did receive a positive clinical signal. If there were two P2 trials with conflicting results (one positive and one nonpositive) the P3 trial was put into this group.

If a matched P2 trial did not have a positive primary clinical efficacy endpoint, it was called **ambiguous**. This group included trials that were nonpositive on their primary clinical efficacy endpoint, or had a primary endpoint investigating biomarkers, safety, etc. Often times, these phase 2 trials had secondary efficacy endpoints that provided some efficacy data. Trials labeled as “futility trials” were put into this group.

P3 Trials

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

* True bypass: No phase 2 trial in the drug and indication (no match)
* Ambiguous P2 evidence
* Proceeded by positive P2 trial

Extraction

* Termination status
  + And whether it was due to futility or safety concerns. This was found on registration records or in publications
* 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
    - Took the one that is first for hierarchical testing. If there truly was not one higher priority we took the higher dose.
  + 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.
    - HD: Unified Huntington's Disease Rating Scale Total Motor Scale (UHDRS-TMS)
      * The total motor score was extracted as this was the only UHDRS subscale reported consistently across publications in our full-text sample.
    - ALS: ALS Functional Rating Scale (ALSFRS)
      * Both the original ALSFRS and revised ALSFRS-R scales were accepted and meta-analyzed with SMD.
  + WdueAE
    - From ct.gov or consort documents in the publications. Where there was disagreement, the publication took priority.
* 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
* Funding (industry vs nonindustry).
  + If no funder was available, we took the sponsor
  + Any industry involvement was classified as industry funded

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