**The Prevalence and Impact of Phase 2 Trial Bypass in Neurology Drug Development**

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**Abstract**

**Introduction**

**Methods**

P3 Trial Sample

The ClinicalTrials.gov search to identify our sample of drugs was constructed using a list of terms for the following determined neurological diseases: Alzheimer's disease, Parkinson disease, Amyotrophic lateral sclerosis, Huntington's disease, Multiple sclerosis (RRMS and PMS), Migraine, Headache, Epilepsy, TBI and Stroke recurrence. All phase 3 trials with actual primary completion dates from January 1, 2011- January 1, 2021 using these terms were downloaded from ClinicalTrials.gov for screening. The end range was chosen to allow one year between primary completion and depositing results as per the Final Rule.21 Our objective is 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. Each trial was screened to ensure it is testing a drug/biologic related to the included neurological conditions.

Inclusion criteria was a) listed in ct.gov as “Phase 3, Phase 2/3, Phase 2b/3. Randomized, parallel group, or sequential, controlled trial; b) control is either placebo or another treatment (not a different dose of same drug; c) must test a drug or biologic; g) 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): f) at least one US or CAD, EU, UK, Australian research site, g) Investigated a treatment for the included neurological conditions either treating the condition itself or a symptom of the condition that is widely used as measure of disease modification of the condition (as determined by consultation with neurologists). The exclusion criteria was a) head-to-head trials of standard of care interventions as the primary analysis, b) primary purpose is diagnostic or screening c) includes healthy volunteers, d) or Withdrawn (i.e. no patients enrolled).

Phase 3 trial publications were first searched for on ClinicalTrials.gov. For ClinicalTrials.gov records where no publication was linked, we conducted Google Scholar and OVID searches to find study publications for each trial. If multiple publications/abstracts were found, the primary publication will be chosen (i.e. the publication that reports full primary-endpoint results). All trials will need to have a publication of their results to be included. Publications only containing interim results will not be used unless the study was terminated at interim analysis.

Matching P3 Trials to Prior P2 Trials

To the introduction, conclusion, and research sections in the Phase 3 publications will be searched for P2 trials. If none meet the matching criteria (see below), we searched TrialViewer (ClinicalTrials.gov) for additional P2 trials. If there are still no matches, we searched for P2 trials using google scholar, MEDLINE and EMBASE via OVID. For approved drugs, drugs@FDA documents will be used to check that we correctly matched P2 trials to P3 trials. As a last resort, corresponding authors or sponsors will be emailed to query about possible phase 2 trials.

To determine if a P2 trial was eligible to be a match, it had to have a primary start date that was one year 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) and investigate the same drug or biologic in the same condition (see supplement for details).

Extractions

From each Phase 2 trial we extracted the positivity, the number of patients, and trial duration. 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. Alternatively, P2 trials were deemed to be ambiguous where a primary endpoint is negative, but a secondary or coprimary was positive, when subgroup analyses are used as the positive signal, or the trial used a biomarker endpoint as their primary outcome.

From each Phase 3 trial we extracted termination status, positivity status, SMD on primary efficacy endpoint (if available), withdrawals due AEs, approval status, funding (industry vs nonindustry), number of patients, trial duration, and phase.

Prevalence of Bypassing

P3 trials were then put into the following groups: Preceded by P2: have a matched P2 trial that is positive per our definition above, ambiguous P2 bypass: Had a matched P2 trial that was nonpositive per our definition above, or true P2 bypass: Did not have a matched P2 trial.

To determine whether bypass was associated with any variables compared the proportions of trials that were not preceded by P2 on the following variables: Funded by industry vs. non-industry, condition was severe vs. non-severe condition (operationalized based on 5-year mortality or disability), and approval status.

Impact of Bypass on Risk and Benefit

Restricting our analysis to those indication areas where there are at least 3 trials in the bypass and non-bypass group and within these indications. We performed a chi-squared test between the proportion of P3 trials in the bypass group vs non-bypass group and the P3: a) rate of termination, b) positivity on the primary endpoint

We performed a pooled meta-analysis with subgroup contrast between the bypass group vs non-bypass group for the following two variables. Pooled SMDs for efficacy outcomes, where trials involve continuous outcomes22 RR for withdrawal related adverse events for all trials in sample.

Within the five disease areas with the largest number of trials in our sample, we will find the average number of patients enrolled in phase 3 trials that are ultimately negative on their primary endpoint or stopped early due to safety or futility that bypassed phase 2 evidence and compare this to the average number of patients in phase 2 trials in our sample. We will present the difference between these averages as the number of patients that could have potentially been spared if bypassing had not occurred (assuming the nonpositive result could have been discovered had a P2 trial been run). We will perform a similar analysis, estimating trial duration (e.g. patient years). In addition, we will estimate the proportion of patients in our sample that were in P3 trials that bypassed.

Statistical Analyses

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**Results**

Sample of Index P3 trials

Prevalence of P2 Bypass

Risk and Benefit of P2 Bypassing

**Discussion**

Limitations

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

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**Data Sharing:** Data will be available on Open Science Framework

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