**The Prevalence and Impact of Bypassing Phase 2 Trials in Neurology Drug Development**

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**Word Count:** ~x

**Abstract**

**Introduction**

Drug development for neurologic disorders is slow, expensive and failure prone. Many neurological disorders are characterized by heterogenous populations and slow progression, thus necessitating lengthy clinical trials enrolling large populations. Uncertainties surrounding pathophysiological processes in neurologic diseases and the severe limitations of animal models further complicate the task of developing effective treatments.

To reduce the expense and time associated with drug development, some sponsors truncate the drug development process by skipping or deprioritizing preliminary evaluation of a drug’s efficacy in phase 2 clinical trials. For example, investigational Alzheimer’s disease treatments Aducanumab1 and Gantenerumab2 were both advanced into pivotal phase 3 trials based on signals from phase 1 trials.Such “phase 2 bypass” may help researchers to overcome the inherent limitations of statistical powering in phase 2 trials and the lack of surrogate endpoints for many neurologic conditions.3,4

However, the risk/benefit balance for phase 3 trials may be impaired when they are started without efficacy evidence from phase 2 trials. For example, when phase 3 trial designers bypass phase 2, they likely have less available evidence to optimize the “intervention ensemble”, i.e. the variables surrounding a treatment that make it effective, such as dose.5 In addition, phase 2 trials can provide drug developers with an opportunity to find futile interventions before moving the treatment into longer and larger phase 3 trials. Therefore, efficacy evidence may be important to collect prior to phase 3 trials in order to “derisk”5 against negative outcomes.6,7

Our team previously reported that nearly half of phase 3 trials investigating treatments for solid tumors bypassed phase 2 trials and that trials that bypassed had significantly worse survival outcomes.8 To the best of our knowledge, no researchers have systematically estimated the proportion of phase 3 trials in neurology that are initiated using various types of evidence. Similarly, the association between phase 2 bypass and phase 3 trial results has yet to be shown.

In the present work, we assess the prevalence with which phase 3 trials in neurology are launched absent affirmative efficacy support from a phase 2 trial. Secondarily, we assess the impact of phase 2 bypass on phase 3 trial outcomes.

**Methods**

Overview

Our primary goal was to estimate the prevalence of phase 2 bypass in ten neurological diseases for a decade of phase 3 trials. We defined phase 2 bypass as any case in which researchers initiated a phase 3 trial without positive surrogate or clinical evidence from a phase 2 trial in the same indication.8 Our secondary goals were to present the proportion of phase 3 trials initiated with three levels of prior evidence, determine whether trial characteristics where associated with phase 2 bypass, and to investigate whether phase 2 bypass impacted phase 3 trial outcomes.

Phase 3 Trial Sample

We created our sample of phase 3 trials using a list of search terms on ClinicalTrials.gov for the following neurological diseases: Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis, Huntington's disease, relapsing multiple sclerosis, progressive multiple sclerosis, headache, epilepsy, traumatic brain injury, and stroke recurrence or recovery. We chose these conditions based on the relatively high volume of clinical trialing in each area. All phase 3 and phase 2 / 3 trials with primary completion dates January 1, 2011- January 1, 2021 were downloaded from ClinicalTrials.gov for screening.

We included trials that: a) tested a drug or biologic; b) had at least one research site in US, Canada, EU, UK, or Australia; and c) involved an intervention that was purportedly disease modifying or that targeted a symptom regarded as a proxy for disease modification typically used as a primary outcome in P3 trials. We excluded trials where: a) the primary purpose was diagnostic or screening; or b) trials were preceded by a phase 3 or 4 trial that started >1 year earlier (see supplemental methods for full inclusion and exclusion criteria).

We searched for phase 3 trial publications on ClinicalTrials.gov, Google Scholar, MEDLINE and EMBASE. If we were unable to find any publication, we used results deposited on ClinicalTrials.gov for our analysis.

Matching Phase 3 Trials to Prior Phase 2 Trials

For every phase 3 trial in our sample, we searched for “matched” phase 2 trials using references in published phase 3 trials, by searching ClinicalTrials.gov, and using Drugs@FDA (for drugs that received approval). A phase 2 trial was considered to match a phase 3 trial in our sample if: 1) it investigated the same treatment in the same condition and 2) the phase 2 trial started at least one year earlier than the phase 3 trial. When we could not find any matched phase 2 trials, corresponding authors of phase 3 trial results were queried by email.

Extractions

We extracted the following items from phase 3 trials: a) completion status; b) the outcome on the primary endpoint; c) the proportion of patients who withdrew due adverse events in each arm; d) the approval status of the experimental treatment in any indication at the time of trial indication; e) funding (industry or non-industry); and f) phase (2/3 or 3).

We extracted the following items from all matched phase 2 trials: a) whether the primary endpoint was a clinical or a reasonably validated efficacy surrogate endpoint; and b) the outcome on the primary endpoint. Neurologist co-authors (EA and LS) and additional neurologists provided input on whether surrogates were reasonably validated.

Prevalence of Phase 3 Bypass

Our primary outcome was the prevalence of phase 2 bypass across all neurological indications in our sample. We calculated the proportion of phase 3 trials that were launched using three different levels of phase 2 evidence: 1) preceded by a phase 2 trial that was positive on a primary clinical or validated surrogate endpoint (“non-bypass”); 2) preceded by an phase 2 that provided evidence other than that from primary efficacy result (“ambiguous”). This category was split into: a) preceded by a phase 2 trial that was non-positive on clinical or validated surrogate endpoints (non-positive); and b) preceded by a phase 2 trial that investigated proof of concept endpoints, only investigated safety, or used non-validated surrogate endpoints (“not focused on efficacy”). The final category was: 3) not preceded by a phase 2 trial in the same indication with the same drug (“true bypass”). For our purposes, all trials that were not in the first category were deemed to have bypassed phase 2.

We also tested whether phase 2 bypass was associated with phase 3 trial characteristsindustry funding, the approval status of the experimental treatment at the time of trial initiation, or primarily degenerative conditions (Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis, Huntington's disease, and progressive multiple sclerosis) using Fisher-exact tests. We included two additional post-hoc analyses investigating whether phase 3 sample size or trial duration were greater in phase 3 trials that bypassed phase 2.

Impact of Bypass on Phase 3 Trial Results

As a secondary analysis, we investigated whether phase 2 bypassing was associated with three adverse outcomes: 1) a diminished proportion of positive phase 3 trial results; 2) an increased proportion of phase 3 that are terminated due safety or futility; and 3) an increased risk to patients participating in the phase 3 trials (using within trial risk ratios (RR) for withdrawal-related adverse events (WdAEs)).

Statistical Analysis

We used Fisher-exact tests to investigate whether three P3 trial characteristics and two P3 trial results were associated with phase 2 bypass. In addition, we compared P3 trial sample sizes and trial duration between trials that bypassed and those that did not using paired t-tests. To compare whether risk of withdrawal due to adverse events was impacted by bypassing, we pooled RRs in a meta-analyses with subgroup contrasts between phase 3 trials that bypassed and those that did not. We used the two-tailed *p-*value of Cochran's Q for subgroup difference to investigate significance. We did not adjust for multiple hypothesis testing. We determined significance using a nominal significance level of 0.05 for all analyses.

See supplement for more methodological details and protocol deviations. All extractions were performed in duplicate, and consensus was sought from JK. Our protocol was registered at <https://osf.io/crf62/>

**Results**

Sample of Index Phase 3 trials

A total of 113 phase 3 trials were included ( **Figure 1**). Together, Alzheimer’s disease (n = 30, 27%), and headache (n = 26, 23%) accounted for the majority of trials. Most trials were funded by industry (n = 94, 83%) and were investigating treatments that were not approved in any indication (n = 92, 81%) at the time of trial initiation (**See Table 1).**

Prevalence of Phase 2 Bypass

Overall, 53 phase 3 trials (47%) were scored as having bypassed positive efficacy results from a phase 2 trial. The most common form of bypass was true bypass (n = 21, 19%). Among disease areas with more than ten trials in our sample, phase 2 bypass was most common in Alzheimer’s disease trials (n= 19, 63%) and least common in trials investigating treatments for relapsing multiple sclerosis (n=1, 6%) (**see** **Table 2).**

Phase 2 bypass was not significantly associated with industry funding: 77% (n=40) of trials that bypassed phase 2 were funded by industry compared to 89% (n=54) in trials that were preceded by phase 2 trials (p=0.13). Similarly, phase 2 bypass was not significantly associated with the investigational drug’s approval status: 23% (n=12) of trials that bypassed were approved in different indications compared to 15% (n=9) of trials that were preceded by phase 2 (p=0.33). Phase 2 bypass was significantly associated with primarily degenerative conditions: 62% (n=32) of trials that bypassed were investigating primarily degenerative diseases compared to 34% (n=21) of trials that did not bypass (p=<0.001). Mean phase 3 trial sample size and duration were not significantly different between trials that bypassed and those that did not (Sample size-1322 vs 1058 patients respectively, p=0.12; Duration-1049 vs 931 days respectively, p=0.63).

Patient Risk and Benefit of Phase 2 Bypassing

Phase 3 trials that bypassed phase 2 were significantly less likely to be positive on their primary outcome than trials that were preceded by positive efficacy evidence from a phase 2 (31%, n=15 vs 57%, n=34 respectively, p=0.01). It should be noted that nonpositive results are common in indications such as Alzheimer’s disease because the disease is not well understood. Therefore, the association between phase 2 bypass and nonpositive results may be the result of confounding factors. The frequency of phase 3 trial termination due to safety or futility was non-significantly higher in the group that bypassed phase 2 (Bypass: 29%, n=15, Non-bypass: 15%, n=9, p=0.11) **(see** **Table 3).** Pooled RRs for withdrawals due to adverse events were not significantly different between trials that bypassed and those that did not (RR=1.46 vs RR=1.36 respectively, p=0.65) (**see** **Figure 2).**

**Discussion: incoming**

**Declaration of Interest:** JK received consulting fees from Amylyx Inc. Authors declare no other potential conflicts of interest.

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

**Acknowledgments:**

**Funding**: This work was funded by CIHR.

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