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

Hannah Moyer, BSc1, Robyn Mellet, BSc1, Karine Vigneault1, Maya McKeown1 Jason Karlawish, MD2, Erika Augustine, MD3, Lon Schneider, MD4, Jonathan Kimmelman, PhD1

1. Department of Equity, Ethics and Policy, McGill University, Montreal, QC Canada

2. University of Pennsylvania…

3. Kennedy Krieger Institute…

4. University of Southern California…

\* Corresponding author. Email: [jonathan.kimmelman@mcgill.ca](mailto:jonathan.kimmelman@mcgill.ca) Phone: (514) 953 3306; 2001 McGill College Ave, Montreal QC, H3A 1G1

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**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 and large populations. Uncertainties surrounding pathophysiology and the severe limitations of animal models further add to the challenges of developing effective treatments for neurologic disease.

To reduce the expense and time associated with testing new neurologic drugs in patients, sponsors sometimes truncate clinical development 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 avoidance of phase 2 testing may help researchers overcome the inherent limitations of statistical powering in phase 2 trials and the absence of validated surrogate endpoints for many neurologic conditions.3,4

However, avoidance of phase 2 testing is controversial. Risk/benefit balance for phase 3 trials may be impaired when they are started without supporting evidence from phase 2 trials. For example, when sponsors bypass phase 2, they have less information for optimizing variables like dose or trial eligibility for the phase 3 trial5 In addition, phase 2 trials provide sponsors an opportunity to eliminate flagging drug candidates before they are advanced to longer and larger phase 3 trials. Therefore, efficacy evidence may be important to collect prior to phase 3 trials in order to reduce the prospect of negative outcomes.5,67

In what follows, we define “phase 2 bypass” as the launch of phase 3 trials absent phase 2 testing for efficacy, or despite negative outcomes in such testing. Our team previously reported that nearly half of phase 3 trials for solid tumor treatments bypassed phase 2 trials and that trials that bypassed had significantly worse survival outcomes.8  In the present work, we assess the prevalence and impact of phase 2 bypass in neurologic drug development.

**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 types of phase 2 bypass, identify factors associated with phase 2 bypass, and to investigate whether phase 2 bypass affected 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.

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, searches of ClinicalTrials.gov, and using Drugs@FDA (for drugs that received approval). Phase 2 trials were considered to match a phase 3 trial in our sample if: 1) they 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 support: 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 efficacy-centered”). The final category was: 3) not preceded by a phase 2 trial in the same indication with the same drug (“full 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 the following characteristics of phase 3 trials: industry funding, the approval status of the experimental treatment in a different indication 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). 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 Outcomes

As a secondary analysis, we investigated whether phase 2 bypass was associated with three unfavourable outcomes: 1) a diminished proportion of positive phase 3 trial results; 2) an increased proportion of phase 3 trials that are terminated due safety or futility; and 3) increased risk to patients, using within trial risk ratios (RR) for withdrawal-related adverse events (WdAEs)). We performed a sensitivity analysis to investigate whether phase 2 bypass was associated with phase 3 positivity when we exclude indications with near universal nonpositive (<15%) or positive (>85%) results.

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.

Our protocol was registered at <https://osf.io/crf62/>. See supplement for more methodological details, screening criteria, 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 full 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). When we excluded indications with near universal positivity (RMS and PMS) or non-positivity (Stroke, TBI, HD, and AD), this effect was not present (p=>.99). The frequency of phase 3 trial termination due to safety or futility was non-significantly higher in the group that bypassed phase 2 (29%, n=15 for P2 bypass vs. 15%, n=9 for P2 non-bypass, p=0.11) **(see** **Table 3** and **supplementary Table 1** for indication specific results). 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** **supplementary Figure 1).**

**Discussion:**

Phase 2 bypass was common (47%) in our sample of phase 3 trials investigating treatments for neurologic conditions. Furthermore, phase 3 trials launched without positive clinical or validated surrogate evidence from phase 2 trials were significantly less likely to have a positive result and insignificantly more likely to be terminated due to safety concerns or futility analyses. However, researchers may bypass phase 2 for many reasons, some justifiable.

To start, there are a few scientific and statistical reasons that bypassing phase 2 trials may be appropriate. For example, researchers investigating treatments for many neurologic conditions lack surrogate endpoints with clear associations with clinical outcomes. Therefore, phase 2 trials in these indications may be less useful than in indications that have outcomes which can provide quick read-outs of efficacy information. In addition, the outcomes that are used for some conditions need large numbers of patients to detect differences or lengthy trials to see long-term safety/efficacy outcomes.7 In our sample, we found that bypassing was more common in degenerative diseases, which likely suffer from both of the challenges described above. However, trials in all conditions in our sample both bypassed and did not, suggesting that it is in fact possible to run phase 2 trials focused on collecting efficacy before phase 3 trials, even in these problem areas. In addition, we did not find that phase 2 bypassing was associated with increased phase 3 trial duration or sample size.

Secondly, the current costs for developing new neurologic drugs are unsustainable, and funders need to invest in each clinical trial wisely. One way for pharmaceutical companies to save cost and time in drug development would be bypass phase 2 trials. A recent analysis of Alzheimer’s clinical trials found that phase 3 trials were more than double as expensive and long as phase 2 trials. Bypassing phase 2 trials in this case would cut their costs up to 10 million per drug-indication pairing.8 Though commercial reasons undoubtedly influenced some instances of phase 2 bypass in our sample, we did not find that bypassed trials were more likely to be industry funded. //OPPORTUNITY COST stuff//if it is not positive may need to go back.

Thirdly, researchers may bypass phase 2 trials when repurposing an already approved drug in a new indication. In these cases, trial designers have already collected evidence on safe dose ranges, pharmacokinetics, and safety concerns in large numbers of patients. However, patients with different conditions can respond very differently to the same treatment and reviews have suggested that researchers should use repurpose by putting drugs into phase 2 trials first.9 In our sample, we found that phase 3 trials that bypassed were no more likely to have been approved in other indications at the time of initiation. However, numerically, repurposing was most common in trials in that fully bypassed phase 2 trials.

Transition to discussion of p3 trial results… .

We found that, across all indications in our sample, phase 3 trial positivity was significantly lower in the group of trials that bypassed positive efficacy evidence from phase 2 trials. However, this association may be the result of confounding factors that both influence the decision to bypass and the likelihood that the phase 3 trial is positive, such as the presence of surrogate endpoints and the level to which disease pathology is understood. To isolate the impact of bypassing on phase 3 trial positivity, we performed a sensitivity analysis without the conditions that had near universal positivity or non-positivity (<15% or >85%). In the remaining four indications (46 trials) we did not see an association between bypassing phase 2 and the proportion of phase 3 trials that were positive.

In addition, our analysis comparing phase 3 outcomes with different types of phase 2 bypass results revealed the following trends. Firstly, we found that, numerically, phase 3 trials initiated after an ambiguous phase 2 trial were less likely to have a positive result than phase 3 trials that fully bypassed. This trend implies that phase 2 trials that provided information other than primary efficacy evidence, such as dose and population details, did not increase the likelihood of phase 3 positivity compared to instances of full bypass. Rather, primary positive efficacy evidence from phase 2 trials may be the important variable to collect from phase 2 trials. Secondly, phase 3 trials started after non-positive results from phase 2 trials were especially likely to be terminated. Therefore, phase 2 trials may be especially useful as a go/no go step to stop investigating futile or unsafe treatments in neurologic drug development.

Limitations

Our results should be interpreted with the following limitations. First, we pooled positivity and termination rates across neurologic diseases with vastly different rates for these outcomes because we were limited by our sample sizes within indications. Second, we were not always able to find publications or results for potential phase 2 matches. In these cases, we may have characterized trials as having bypassed when there was a trial available that only phase 3 trial designers had access to. Third, some publications for earlier trials did not use phased languages. When this happened, we used algorithmic rules to designate a phase number and were occasionally forced to rely on sample size. Fourth, positivity is a reductive measure of trial success.

Conclusion

Taken together, our findings suggest that bypassing positive efficacy evidence from phase 2 trials is common in neurologic drug development. Although there are cases in which bypassing phase 2 trials may be appropriate, this practice may diminish the likelihood that the subsequent phase 3 trial will be positive. Further work is needed to explore varying criteria to inform a more sustained discussion of the appropriateness of phase 2 bypassing in neurology.

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

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