**The Prevalence and Impact of Bypassing Phase 2 Trials for Pivotal Trials in Neurologic Drug Development**

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**Abstract**

Objective:

Pivotal trials for new neurologic drugs are often launched absent support from prior, positive phase 2 trials. Our primary objective was to determine the prevalence of such “phase 2 bypass” in neurologic drug development.

Methods:

We used ClinicalTrials.gov to create a sample of phase 3 trials that were investigating treatments for ten neurologic conditions and that were completed between 2011- 21. We then searched backwards to find phase 2 trials involving the same drug-indication pairing to determine whether the phase 3 trial bypassed phase 2 testing. Secondarily, we investigated circumstances where phase 2 bypass was more prevalent, and whether phase 2 bypass was associated with adverse phase 3 trial outcomes.

Results:

We included 113 phase 3 trials in our sample, 47% of which bypassed positive efficacy evidence from a phase 2 trial. The prevalence of phase 2 bypass varied across indications, with bypass most prevalent in Alzheimer’s disease (63%) and least prevalent in relapsing-remitting multiple sclerosis (6%). Phase 2 bypass was not associated with industry funding or drug repurposing trials. Overall, phase 3 trials in our sample were significantly less likely to be positive on their primary outcome and non-significantly more likely to have terminated early due to safety or futility.

Conclusion:

Almost half of neurologic disease phase 3 trials are launched absent supporting evidence from positive phase 2 trials. Our findings regarding the impact of phase 2 bypass on phase 3 outcomes were inconclusive. However, we urge development of criteria that define when the risks of phase 2 bypass are acceptable.

**Introduction**

Drug development for neurologic disorders is slow, expensive and failure prone. Many neurological disorders are characterized by heterogeneous populations and slow progression, thus necessitating lengthy clinical trials and large populations.1–4 Uncertainties surrounding pathophysiology and the severe limitations of animal models further add to the challenges of developing effective treatments for neurologic disease.5–7

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 Aducanumab8 and Gantenerumabwere 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 trials10 and the absence of validated surrogate endpoints for many neurologic conditions.6,11

However, forgoing phase 2 testing is controversial.1,12–15 Risk/benefit balance for phase 3 trials may be degraded 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 trial.5 In addition, phase 2 trials provide sponsors an opportunity to eliminate flagging drug candidates before they are evaluated in longer and larger phase 3 trials.

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 efficacy 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’s 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 phase 3 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. When we were unable to find publications, 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, ClinicalTrials.gov, and 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 to adverse events in each arm; d) the approval status of the experimental treatment in any indication at the time of trial initiation; 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 2 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 a phase 2 that provided evidence other than that from primary efficacy result (“ambiguous”). The ambiguous 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’s 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 to safety or futility; and 3) increased risk to patients, using within trial risk ratios (RR) for withdrawal-related adverse events (WdAEs). As a post-hoc sensitivity analysis to further probe the impact of phase 2 bypass, we tested whether phase 2 bypass was associated with phase 3 positivity when we excluded indications with near universal non-positive (<15%) or positive (>85%) results.

Statistical Analysis

We used Fisher-exact tests to investigate whether three phase 3 trial characteristics and two phase 3 trial results were associated with phase 2 bypass. In addition, we compared average phase 3 trial sample sizes and trial durations 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-analysis 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.

**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 the 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, 52 phase 3 trials (46%) were scored as having bypassed positive efficacy results from a phase 2 trial. The most common form of bypass was full bypass (n = 20, 18%). 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) of 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) (**Table 3**). Phase 3 trials investigating treatments for primarily degenerative conditions were significantly more likely to bypass phase 2 than trials in nondegenerative conditions: 61% (n = 32) of trials investigating primarily degenerative diseases bypassed phase 2 compared to 33% (n = 20) of trials investigating nondegenerative conditions (p =< 0.005). 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 trial (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 (61%, n = 11 for phase 2 bypass vs 61%, n = 17 for phase 2 non-bypass, > .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 phase 2 bypass vs 15%, n = 9 for phase 2 non-bypass, p = 0.11)(**see** **Table 3** and **eTable 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** **eFigure 1**).

**Discussion:**

Phase 2 bypass was common (46%) in our sample of phase 3 trials investigating treatments for neurologic conditions. Phase 3 trials for primarily degenerative diseases were more likely than not to bypass phase 2 trials. In contrast, phase 3 trials in relapsing-remitting multiple sclerosis rarely employed phase 2 bypass.

Phase 2 trials play a crucial role in providing a scientific and ethical justification for phase 3 testing. They provide opportunities for sponsors to find dosing or patient populations that maximize the prospect of attaining a positive result in pivotal trials. By probing efficacy, they may also play a key role in increasing the prior probability that a phase 3 trial will produce a positive result. Ethically, phase 2 trials help establish the basis for clinical equipoise in phase 3 trials, and minimize the prospect that patients receive prolonged exposure to a futile drug.

However, sponsors might defend phase 2 bypass in three ways. First, sponsors may prefer to put a drug candidate directly into phase 3 testing to reduce the costs and time needed to obtain regulatory approval. Second, sponsors might argue that phase 2 testing is not necessary for trials testing repurposed drugs. In such circumstances, researchers may be able to use evidence from other indications to establish safety and target engagement. Third, sponsors might defend phase 2 bypass by appealing to scientific feasibility. For example, in research areas where there are no validated surrogate endpoints, sponsors may face difficulty designing phase 2 trials that are smaller and shorter than a phase 3 study, but that are adequately powered to detect efficacy. In such cases, sponsors may opt to use the interim analysis of a phase 3 trial as a substitute for phase 2 trials.

Our findings do not suggest that any of the above explanations predominate. To the argument for cost reduction, we found no relationship between phase 2 bypass and industry sponsorship. Nor was bypass more prevalent with repurposed drugs. Scientific feasibility for indications in our sample is suggested by the fact that, in all indications, there were at least some phase 3 trials that were preceded by positive phase 2 trials. The scientific feasibility of running phase 2 trials in the indication areas we surveyed is also underscored by the fact that phase 2 bypass was not more prevalent in indication areas that involve larger sample sizes or greater duration for phase 3 trials.

However, our findings are equivocal as to whether current practices of phase 2 bypass are harmful. On the one hand, our analyses suggest that phase 3 trials launched without positive clinical or validated surrogate evidence from phase 2 trials have more adverse outcomes, as indicated by greater prospect of early termination and significantly greater prospect of negative primary outcomes. However, the patterns we observe may represent the confounding effect of indications in our sample. For example, trials for Alzheimer’s disease accounted for 37% of phase 3 trials that bypassed in our sample. Alzheimer’s disease lacks validated surrogate endpoints for phase 2 trials, and Alzheimer’s disease phase 3 trials in our sample were almost all negative on their primary outcome. When we performed an analysis only within indications where primary outcomes in phase 3 trials were variable, we no longer observed an association between phase 2 bypassing and trial negativity.

Our analyses provide some clues as to where phase 2 trials deliver the greatest value. 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, may not have increased the probability of phase 3 positivity. 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 for data monitoring in phase 3 trials (?) as a go/no go step to stop investigating futile or unsafe treatments in neurologic drug development.

Limitations

Our study has 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. This introduced a source of confound into our analysis of the impact of phase 2 bypass. Second, some publications for earlier trials did not define their phase. When this happened, we assigned phase based on a set of prespecified rules. Third, positivity is a reductive measure of trial success. Fourth, a planned meta-analysis to measure the impact of phase 2 bypass on efficacy effect sizes could not be completed due to an insufficient sample of trials in different indications. Our ability to assess adverse impacts of phase 2 bypass is limited by the effects of confounds described above.

Conclusion

Our findings suggest that bypassing positive efficacy evidence from phase 2 trials is common in neurologic drug development. However, neither commercial motivation, repurposing approved drugs, or scientific feasibility appears to dominate the reasons for bypass. While logic and studies in other areas suggest that patients and trial outcomes are adversely affected by phase 2 bypass,16 the present analysis does not establish worse outcomes for patients when phase 3 trials are launched absent supporting phase 2 evidence. Given the prevalence of phase 2 bypass and the adverse outcomes of bypass in other disease areas, we urge the development of formal criteria for deciding when phase 2 bypass in neurological drug development is justified.

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

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**Tables and Figures**

**Table 1. Characteristics of the Phase 3 Trial Sample**

|  |  |
| --- | --- |
| Indications | Number of phase 3 trials  N=113 (%) |
|
|
| Indication |  |
| Alzheimer's disease | 30 (27) |
| Parkinson's disease | 10 (9) |
| Amyotrophic lateral sclerosis | 5 (4) |
| Huntington's disease | 4 (4) |
| Relapsing Multiple sclerosis | 16 (14) |
| Progressive Multiple sclerosis | 4 (4) |
| Headache | 26 (23) |
| Epilepsy | 7 (6) |
| TBI | 5 (4) |
| Stroke | 6 (5) |
| All | 113 |
| General |  |
| Pharmaceutical funder | 94 (83) |
| Pre-approval status | 92 (81) |
| Positive primary endpoint | 49 (45)\* |
| Terminated for safety or futility | 24 (21) |
| Median sample size (IQR) | 835 (706) |
| Median trial duration in years (IQR) | 2.92 (1.97) |

\*Out of 108 trials with primary results available

**Table 2. Prevalence of Bypassing**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Indications | Overall  (N) | Non-Bypass | Bypass | | |
| **Preceded by Positive Phase 2**  **(N, %)** | **Preceded by Ambiguous Phase 2**  **(N, %)** | | **Full Bypass**  **(N, %)** |
| **Non-Positive** | **Not Efficacy-Centered** |
| Alzheimer's disease | 30 | 11 (37) | 6 (20) | 7 (23) | 6 (20) |
| Parkinson's disease | 10 | 5 (50) | 0 (0) | 4 (40) | 1 (10) |
| Amyotrophic lateral sclerosis | 5 | 3 (60) | 2 (40) | 0 (0) | 0 (0) |
| Huntington's disease | 4 | 1 (25) | 2 (50) | 1 (25) | 0 (0) |
| Relapsing multiple sclerosis | 16 | 15 (94) | 0 (0) | 1 (6) | 0 (0) |
| Progressive multiple sclerosis | 4 | 1 (25) | 1 (25) | 1 (25) | 1 (25) |
| Headache | 26 | 19 (73) | 4 (15) | 0 (0) | 3 (12) |
| Epilepsy | 7 | 2 (29) | 1 (14) | 0 (0) | 4 (57) |
| TBI | 5 | 3 (60) | 0 (0) | 1 (20) | 1 (20) |
| Stroke | 6 | 1 (17) | 1 (17) | 0 (0) | 4 (67) |
| All indications | **113** | **61 (54)** | **17 (15)** | **15 (13)** | **20 (18)** |

**Table 3. Relationship between Phase 2 Bypass and Phase 3 Trial Characteristics / Results**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Non-Bypass | Bypass | | | P-values  Non-Bypass vs Bypass1 |
| **Preceded by Positive Phase 2**  **N (%)** | **Preceded by Ambiguous Phase 2**  **N (%)** | | **Full Bypass**  **N (%)** |
| **Non-Positive** | **Not Efficacy-Centered** |
| Trial Characteristics |  |  |  |  |  |
| Pharmaceutical Funder | 54/61 (89) | 16/17 (94) | 10/15 (67) | 14/20 (70) | 0.13 |
| Approved | 9/61 (15) | 2/17 (12) | 2/15 (13) | 8/20 (40) | 0.33 |
| Phase 3 Trial Results |  |  |  |  |  |
| Positivity Proportion2 | 34/60 (57) | 4/17 (24) | 3/14 (21) | 8/17 (47) | 0.01 |
| Termination Proportion | 9/61 (15) | 6/17 (35) | 3/15 (20) | 6/20 (30) | 0.11 |

1Fisher-exact test between trials in non-bypassed trajectories vs bypassed trajectories (Preceded by Ambiguous Phase 2 and Full Bypass trials)

2Trials were only included in the positivity analysis if they had primary results available (N = 108)

**Figure 1. Prisma Flow Diagram for the Phase 3 Trial Sample**