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

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**Abstract**

**Introduction**

ONE APPROACH Drug development in neurology has one of the highest rates of failure across medicine.

One approach to reducing timelines for drug development in neurology is by truncating the drug development process. New drug are typically evaluated first in phase 1 trials for safety and dosage. Promising drug are then evaluated for evidence of efficacy- typically using surrogate endpoints and/or

for neurologic conditions typically involves three sequential phase s of clinical trials aimed at gaining FDA approval for new treatment options. Phase 1 (P1) trials are primarily focused on gathering pharmacological information. Next, phase 2 (P2) trials usually aim to understand safety, optimize dose/schedule, and begin to investigate efficacy. Together, P1 and P2 trials are called the “learn zone” of clinical research and support later trial designs.1 Finally, phase 3 (phase 3) trials focus on confirming efficacy and safety in large numbers of patients on the treatment for long periods of time.

Throughout these phase s, neurologic drug development suffers from a variety of challenges. For example, researchers have trouble ensuring that the drug is transported across the blood-brain barrier, often rely on endpoints that lack validation, and must navigate the long nature of the conditions and treatments. Therefore, investigational treatments for many neurologic conditions have a low chance of resulting in a new approval.2–45,67 The inadequate treatment landscape underlines the need for innovative modifications to the drug development process to get treatments to patients as quickly as possible.

One method used by researchers to accelerate drug development is to initiate phase 3 trials without positive evidence from a P2 trial. We call this strategy “P2 bypass.”8 This practice has been discussed in the literature,9,10 although it is unclear how prevalent it is in neurologic drug development. For example, some reviews have called it “rare,”11 while others mention that it is a strategy used by “many” sponsors.12 In cancer drug development, we found that nearly half of phase 3 trials investigating treatments for solid tumors bypassed P2.8

Relative to the traditional method of running P2 trials prior to phase 3, P2 bypass may accelerate drug development when phase 3 trial results turn out to be positive. However, many questions remain when a phase 3 trial is nonpositive after bypassing. For example, researchers may be unclear as to whether the nonpositive result was due to the lack of optimization of the “intervention ensemble”- the collection of information about a treatment that make it effective5 - or because they were investigating a truly ineffective treatment. If the latter was true, P2 trials may have been able to indicate that the treatment was not likely to be effective earlier in the development process.14,1511,16 In addition, clinical equipoise may be threatened for a phase 3 trial designed with little prior evidence,13 as we found in our investigation of P2 bypass in oncologic drug development.8

In what follows, we report the prevalence of P2 bypass for drug development in ten neurological conditions. Secondarily, we investigated the relationship between P2 bypass and phase 3 trial outcomes.

**Methods**

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, TBI and Stroke. We chose these disease areas because of the volume of clinical research for each as well as the existence of literature on drug development in these areas. 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.

Inclusion criteria were a) treatment involving a drug or biologic; b) at least one research site in US, Canada, EU, UK, or Australia, and c) involving an intervention that is purportedly disease modifying or that targets a symptom regarded as a proxy for disease modification. We excluded trials where: a) the primary purpose was diagnostic or screening; b) trials were preceded by a phase 3 or 4 trial that started >1 year earlier.

We first searched for phase 3 trial publications on ClinicalTrials.gov. When publications were not linked, we conducted searches on Google Scholar and OVID (MEDLINE and EMBASE). If we were unable to find any publications, we used results deposited on ClinicalTrials.gov.

Matching Phase 3 Trials to Prior Phase 2 Trials

For every phase 3 trial in our sample, we searched for “matched” phase 2 trials. A phase 3 trial was considered to have a phase 2 match if: 1) if it investigate the same treatment in the same condition and 2) the phase 2 started at least one year earlier than the phase 3 trial Potential matches were sought using references in phase 3 trial publications, ClinicalTrials.gov, and @accessFDA searches. When we could not find any matched phase 2 trials, corresponding authors of phase 3 trial results were queried.

Extractions

We extracted from each phase 3 in our sample it’s completion status, primary outcome positivity status, the proportion of patients who withdrew due adverse events in each arm, approval status for any indication at the time of trial indication, funding (industry vs non-industry), and phase (2/3 or 3).

We extracted the following items from all P2 trials that were deemed matches for phase 3 trials: [nothing extracted at all?]. We also determined the positivity status of all matched phase 2 trials based on whether trials a) used a primary clinical or reasonably validated efficacy surrogate endpoint, and b) whether the trial was deemed to have refuted the null hypothesis on the primary endpoint. Neurologist co-authors (initials) and additional neurologists provided input on whether surrogates were reasonably validated.

Prevalence of Phase 3 Bypass

Our primary outcome was the prevalence of P2 bypass across all neurological indications in our sample. We calculated the proportion of phase 3 trials that were launched using three different levels of evidence: 1) Preceded by a P2 trial that was positive on a primary clinical or validated surrogate endpoint; 2) Preceded by an P2 that provided evidence other than that from primary efficacy result (Ambiguous). This category was split into two: a) Preceded by a P2 trial that was non-positive on clinical or validated surrogate endpoints and b) Preceded by a P2 trial that investigated proof of concept endpoints, only investigated safety, or used non-validated surrogate endpoints; and 3) phase 3 trials were not preceded by a P2 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 P2.

We also tested whether P2 bypass was associated with industry funding or the approval status of the experimental treatment at the time of trial initiation using a Fisher-exact test.

Impact of Bypass on Phase 3 Trial Results

As a secondary analysis, we investigated whether bypassing positive clinical evidence from P2 trials was associated with phase 3 trial results. We performed a Fisher-exact test to determine whether bypassing impacted the rate of positivity on phase 3 primary outcomes or phase 3 termination due safety or futility. Finally, we performed a pooled meta-analyses for continuous efficacy endpoints and risk ratios (RR) for withdrawal-related adverse events (WdAEs) with subgroup contrasts between the phase 3 trials that bypassed vs those that did not bypass.

Statistical Analysis

We used Fisher-exact tests to investigate whether two P3 trial characteristics and two P3 trial results were associated with P2 bypass. To compare whether risk of withdrawal due to adverse events was impacted by bypassing, 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 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 P2 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, P2 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).** P2 bypass was not significantly more prevalent when trials were industry funded (Bypass: n=40 , 77%, Non-bypass: n= 54, 89%, p=0.13) or when trials involved a drug already approved for a different indication (Bypass: n=12, 23%, Non-bypass: n= , 15%, p=0.33).

Patient Risk and Benefit of P2 Bypassing

Phase 3 trials that bypassed P2 were significantly less likely to be positive on their primary outcome than trials that were preceded by positive efficacy evidence from a P2 (n=15, 31% vs n=34, 57% respectively, p=0.01). The frequency of phase 3 trial termination due to safety or futility was non-significantly higher in the group that bypassed P2 (Bypass: n=15, 29%, Non-bypass: n=9, 15%, 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 (n=36, RR=1.46 vs n= 51, RR=1.36, p=0.65) (**see** **Figure 2).**

**Discussion**

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

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**Figures and Tables**

**Figure 1** -Prisma Flow Diagram for phase 3 Trial Sample

**Diagram, timeline

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**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 (13) |
| 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 (4) |
| 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) |
| Phase 3 | 100 (88) |
| Median sample size (IQR) | 835 (706) |

\*Out of 108 trials with primary results available

**Table 2. Prevalence of Bypassing**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Indications | Overall  (N) | Non-Bypass | Bypass | | |
| **Preceded by Positive P2**  **(N, %)** | **Preceded by Ambiguous P2**  **(N, %)** | | **True Bypass**  **(N, %)** |
| **Nonpositive** | **Not focused on efficacy** |
| 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) | 21 (19) |

**Table 3. Relationship between P2 Bypass and phase 3 trial characteristics / results**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Non-Bypass | Bypass | | | P-values  non-bypass vs bypass\*\* |
| **Preceded by Positive P2**  **N (%)** | **Preceded by Ambiguous P2**  **N (%)** | | **True Bypass**  **N (%)** |
| **Nonpositive** | **Not focused on efficacy** |
| Trial Characteristics |  |  |  |  |  |
| Pharmaceutical funder | 54/61 (89) | 16/35 (94) | 10/15 (67) | 14/20 (70) | 0.13 |
| Approved | 9/61 (15) | 2/35 (12) | 2/15 (13) | 8/20 (40) | 0.33 |
| Trial Results |  |  |  |  |  |
| Positivity Rate\* | 34/60 (57) | 4/17 (24) | 3/14 (21) | 8/17 (47) | 0.01 |
| Termination Rate | 9/61 (15) | 6/17 (35) | 3/15 (20) | 6/20 (30) | 0.11 |

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

\*\*Fisher-exact test between trials in non-bypassed trajectories vs bypassed trajectories:

**Figure 2: RRs for WdAE Pooled Subgroup Analyses**

Chart

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