**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

**Word Count:** ~x

**Abstract**

**Introduction**

Drug development for neurologic conditions typically involves three sequential phases 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 (P3) trials focus on confirming efficacy and safety in large numbers of patients on the treatment for long periods of time.

Throughout these phases, 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 P3 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 P3 trials investigating treatments for solid tumors bypassed P2.8

Relative to the traditional method of running P2 trials prior to P3, P2 bypass may accelerate drug development when P3 trial results turn out to be positive. However, many questions remain when a P3 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 P3 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 created a sample of P3 trials registered on ClinicalTrials.gov and estimated the prevalence of P2 bypassing in ten neurological conditions. Secondly, we investigated whether P3 trial positivity or termination rates were impacted by three types of P2 bypass. These results will help guide decision-making as to whether bypassing P2 trials is an effective method of developing treatments for patients with neurologic conditions.

**Methods**

P3 Trial Sample

We created our sample of P3 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. All P3 and phase 2 / 3 trials with actual primary completion dates from 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 US or CAD, EU, UK, Australian research site, and c) disease modifying treatment or targeting a symptom that is widely used as measure of disease modification of the condition. We excluded trials where: a) the primary purpose was diagnostic or screening; b) trials were preceded by a P3 or P4 trial that started >1 year earlier.

We first searched for P3 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 P3 Trials to Prior P2 Trials

For every P3 trial in our sample, we searched for “matched” P2 trials. For a P2 trial to be an eligible match for the P3 trials in our sample, it had to 1) have started at least one year earlier than the P3 trial, and 2) investigate the same treatment in the same condition. To find potential matches, we searched references of P3 trial publications and ClinicalTrials.gov for matching P2 trials. If the drug received FDA approval, we searched approval documents. When we could not find any matched P2 trials, corresponding authors or sponsors of P3 trial results were queried.

Extractions

We extracted positivity status from each matched P2 trial. To be deemed “positive”, P2 trials must have had a primary clinical or “validated surrogate” efficacy endpoint and be positive on that endpoint based on what was specified in the trial. We consulted neurologist co-authors and additional neurologists on whether surrogates were considered reasonably validated. The only surrogate that we considered reasonably validated was number of gadolinium-enhancing lesions for multiple sclerosis trials.

From each P3 trial in our sample, we extracted termination status, positivity status, SMD on primary efficacy endpoint, 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.

Prevalence of P3 Bypass

Our primary outcome was to estimate the prevalence of bypassing across neurological indications in our sample. We calculated the proportion of P3 trials that were launched using four 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) P3 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.

As a secondary analysis, we investigated 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 P3 Trial Results and Patient Risk/Benefit

For a secondary analysis, we investigated whether bypassing positive clinical evidence from P2 trials was associated with P3 trial results. We performed a Fisher-exact test to determine whether bypassing impacted the rate of positivity on P3 primary outcomes or P3 termination due safety or futility. Additional secondary analyses included pooled meta-analyses for continuous efficacy endpoints and risk ratios (RR) for withdrawal-related adverse events (WdAEs) with subgroup contrasts between the P3 trials that bypassed vs those that did not bypass.

Statistical Analysis

Fisher-exact tests were performed using the “fisher.test” R function.17 Significance was determined using nominal significance level of 0.05 for all analyses. To compare efficacy outcomes between trials that bypassed and those that did not, we performed a meta-analysis with subgroup contrast. This analysis was restricted to indication areas where there are at least 3 trials in the bypass and non-bypass group that had results using the same scale. The only indication with a sufficient number of trials in each subgroup that reported the same outcome was Alzheimer’s disease. We pooled the available least-squared mean differences for the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) using the function “metagen” from the “meta” R package.18. Finally, to compare whether risk of withdrawal due to adverse events was impacted by bypassing, we used the function “metabin” from the “metafor” R package.19 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.

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 P3 trials

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

Prevalence of Bypassing

Overall, 53 P3 trials (47%) bypassed positive efficacy evidence from a P2 trial. The most common form of bypass was true bypass (19%). This category included all P3 trials that were initiated without a prior P2 trial investigating the same treatment in the same indication (**see** **Table 2).**

Bypassing and P3 Trial Results

The prevalence of P2 bypass was not associated with industry funding or approval status (p= 0.13, p=0.33 respectively). P3 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 (Bypass: 31%, Non-bypass: 57%, p=0.01). The rate of P3 trial termination due to safety or futility was non-significantly higher in the group that bypassed P2 (Bypass: 29%, Non-bypass: 15%, p=0.11) **(see** **Table 3).**

Patient Risk and Benefit of P2 Bypassing

The pooled least-squared mean differences for The Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) were not significantly different between trials that bypassed and those that did not (p=0.83) (**see** **Figure 2)**. Similarly, pooled RRs for withdrawals due to adverse events were not significantly different between trials that bypassed and those that did not overall or within subgroups (Overall: p=0.65, Alzheimer’s disease: p=0.91, Headache: p=0.22) (**see** **Figure 3).**

**Discussion**

**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.

**Figures and Tables**

**Figure 1** -Prisma Flow Diagram for P3 Trial Sample

**Diagram, timeline

Description automatically generated**

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

|  |  |
| --- | --- |
| Indications | Number of P3 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 P3 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:

**Chart, box and whisker chart

Description automatically generatedFigure 2: SMDs for ADAS-Cog Pooled Subgroup Analysis.**

**Figure 3: RRs for WdAe Pooled Subgroup Analyses**

