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

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**Abstract**

**Introduction**

The dismal treatment landscape for neurological conditions calls for new and creative ways of modifying the drug development process to get treatments to patients faster and to increase the incentives for companies to invest in their development without putting large numbers of patients and money into futile trials. One such trajectory, bypassing phase 2 (P2) trials, is a possible method to get drugs to patients faster. P2 bypass is defined for our purposes as the practice of initiating phase 3 (P3) trials without positive evidence from a P2 trial.

However, bypassing P2 trials and the information gained from them may impact the future of the drug development trajectory because P3 trials are started with a lower amount of evidence available on efficacy, dose, and population details. In cancer drug development we found that nearly half of P3 trials investigating treatments for solid tumors bypassed P2 and there that was a worse risk/benefit ratio for patients involved in P3 trials that bypassed.1

In what follows, we will first estimate the prevalence of bypassing in ten neurological conditions using four different trajectory types. Secondly, we will investigate how bypassing positive clinical evidence impacts P3 trial success. These results will help guide the decision-making as to whether bypassing P2 trials is appropriate.

P1, P2, P3 in neurolgy. P2 is called the “learn zone” of clinical research and lead to support for P3 trial.1The dismal neurologic drug development landscape calls for empirical analyses of different development trajectories to find the optimal way to develop novel neurological drugs within the constraints of limited resources, such as money or patients. One such trajectory, bypassing P2 trials, is a possible method for speeding up development to get drugs to patients faster.

Although some have discussed the presence of bypassing in neurology, it is still being determined how common this is. There is literature discussing the precedence of P2 bypass in neurology,2,3 although its prevalence has been described variably as “rare”4, or “many”.5 ok no

In what follows, we will describe the prevelance in which P3 trials in ten neurological indications are initated on positive clinical P2 trials, nonpositive trials, trials not aimed at efficacy, and that fully bypassed any P2 results. Then, using positivity and termination rates of P3 trials in each category, we will learn how each level of evidence prepares the P3 trial for success. Maybe we need long trials looking at “medically meaningful” results such as clinical or validated surrogate measures.6 Alternatively, proof of concept P2 trials may be enough to start a P3 trial without sacrificing efficacy.7 These results will help guide the decision-making as to whether bypassing P2 trials is appropriate. Secondary analyses will evaluate whether bypassing is more prevalent in indications more desperate for treatment like AD vs. MS and migraine. There may be a difference in the rate of bypass between disease types because speed may have a different amount of influence on drug development in areas with established standards of care.

**Methods**

P3 Trial Sample

The ClinicalTrials.gov search to identify our sample of trials was constructed using a list of terms for the following determined neurological diseases: Alzheimer's disease, Parkinson disease, Amyotrophic lateral sclerosis, Huntington's disease, Relapsing Multiple Sclerosis, Progressive Multiple Sclerosis, Headache, Epilepsy, TBI and Stroke recurrence. All phase 3 trials with actual primary completion dates from January 1, 2011- January 1, 2021 using these terms were downloaded from ClinicalTrials.gov for screening.

Inclusion criteria was a) listed in ct.gov as “Phase 3, Phase 2/3, Phase 2b/3. Randomized, parallel group, or sequential, controlled trial; b) control is either placebo or another treatment (not a different dose of same drug; c) must test a drug or biologic; g) must be the first phase 3 trial for the treatment/indication pair registered on clinicaltrials.gov (unless there are phase 3 trials that are started within a year of each other and not completed): f) at least one US or CAD, EU, UK, Australian research site, g) Investigated a treatment for the included neurological conditions either treating the condition itself or a symptom of the condition that is widely used as measure of disease modification of the condition (as determined by consultation with neurologists). The exclusion criteria was a) head-to-head trials of standard of care interventions as the primary analysis, b) primary purpose is diagnostic or screening c) includes healthy volunteers, d) or Withdrawn (i.e. no patients enrolled).

Phase 3 trial publications were first searched for on ClinicalTrials.gov. For ClinicalTrials.gov records where no publication was linked, we conducted Google Scholar and OVID searches to find study publications for each trial. If multiple publications/abstracts were found, the primary publication will be chosen (i.e. the publication that reports full primary-endpoint results). All trials will need to have a publication of their results to be included. Publications only containing interim results will not be used unless the study was terminated at interim analysis.

Matching P3 Trials to Prior P2 Trials

The introduction, conclusion, and research sections in the Phase 3 publications were searched for P2 trials. If none meet the matching criteria (see below), we searched TrialViewer (ClinicalTrials.gov) for additional P2 trials. For approved drugs, drugs@FDA documents will be used to check that we correctly matched P2 trials to P3 trials. As a last resort, corresponding authors or sponsors will be emailed to query about possible phase 2 trials.

To determine if a P2 trial was eligible to be a match, it had to have a primary start date that was one year earlier than primary start date of the phase 3 study in our sample, as indicated by ClinicalTrials.gov (or the recruitment start date of the publication if registration date was unavailable) and investigate the same drug or biologic in the same condition

Using three categories to describe the amount of information available before each P3 trial, we will find if they impact positivity and termination rates. The first category is “preceded,” where each trial was preceded by a P2 trial that was positive on a primary clinical or validated surrogate endpoint. The second category is “ambiguous,” where each P3 trial was preceded by a P2 trial that likely provided evidence other than primary efficacy. This category includes two subgroups: “Non-positive,” where P3 trials were preceded by P2 trials that were non-positive on clinical or validated surrogate endpoints, and “Unvalidated endpoint,” where P3 trials were preceded by P2 trials that may have investigated proof of concept endpoints or only investigated safety. The final category is “True bypass,” where all P3 trials were not preceded by a P2 trial in the same indication with the same drug.

Prevalence of Bypassing

To estimate prevalence of bypassing, we found the proportion of P3 trials that were launched using four different trajectories. Trajectories two and three were considered bypassing trajectories for our purposes.

“**Preceded by a positive P2**:” the P3 trial was preceded by a P2 trial that was positive on a primary clinical or validated surrogate endpoint

1. “**Preceded by an Ambiguous P2**:” the P3 trial was preceded by a P2 trial that likely provided evidence other than primary efficacy.

a) “Non-positive:” the P3 trial was preceded by a P2 trial that was non-positive on clinical or validated surrogate endpoints.

b) “Not focused on efficacy:” the P3 trial was preceded by a P2 trial that investigated proof of concept endpoints, only investigated safety, or used non-validated surrogate endpoints.

“**True bypass**”: the P3 trial was not preceded by a P2 trial in the same indication with the same drug

When trying to determine whether a P2 trial could have provided preliminary efficacy evidence for the design of a P3 trial, we wanted to determine which surrogate endpoints we would consider “validated surrogates of efficacy.” These surrogates should and commonly used in phase 2 trials in that indication because of time constraints or other limiting factors. Makes sense mechanistically and has been validated in a P3 trial of a similar drug showing efficacy is associated with it. For example, we considered number of lesions as a validated surrogate endpoint in MS trials. However, we did not consider any AD surrogate endpoint to meet this criterion. The following endpoint is in our sample, and we wondered if you could tell us what you think. You can make notes in the table below:

Extractions

From each Phase 2 trial we extracted the positivity, the number of patients, and trial duration. To be deemed positive, P2 trials must have a primary clinical efficacy endpoint and be positive on that endpoint based on what was pre-specified in the trial. Alternatively, P2 trials were deemed to be ambiguous when a primary clinical endpoint was nonpositive or the trial used a biomarker/safety primary endpoint that is not validated.

From each Phase 3 trial we extracted termination status, positivity status, SMD on primary efficacy endpoint (if available), withdrawals due AEs, approval status, funding (industry vs nonindustry), number of patients, trial duration, and phase.

Prevalence of Bypassing

P3 trials were then put into the following groups: Preceded by P2: have a matched P2 trial that is positive per our definition above, ambiguous P2 bypass: Had a matched P2 trial that was nonpositive per our definition above, or true P2 bypass: Did not have a matched P2 trial.

To determine whether bypass was associated with any variables compared the proportions of trials that were not preceded by P2 on the following variables: Funded by industry vs. non-industry, condition was severe vs. non-severe condition (operationalized based on 5-year mortality or disability), and approval status.

Impact of Bypass on Risk and Benefit

Pos and termination is the most impt because those terminated don’t have results often-

Restricting our analysis to those indication areas where there are at least 3 trials in the bypass and non-bypass group within these indications, we performed a chi-squared test between the proportion of P3 trials in the bypass group vs non-bypass group and the P3: a) rate of termination, b) positivity on the primary endpoint

We also did a broken down analsyis of pos and term rate by trajectory type

We performed a pooled meta-analysis with subgroup contrast between the bypass group vs non-bypass group for the following two variables. Pooled SMDs for efficacy outcomes, where trials involve continuous outcomes8 This was only performed when there were 3 trials in bypassed and 3 trials in non-bypassed group each that had SMD results with the same scale. RR for withdrawal related adverse events for all trials in sample.

Statistical Analyses

DO

See supplement for more methodological details. Protocol registrations

**Results**

Don’t call the preceded group positivity on clinical endpoint-need to say positive on a positive clinical or validated surrogate endpoint.

Sample of Index P3 trials

After applying our inclusion and exclusion criteria, 91 trials were included in our sample. The vast majority of these trials were in Alzheimer’s disease (x), and Headache (x).

Bypassed proportions as per both definitions (preceded vs ambig+bypass) **See Table 1**

Ambigious is imprt bc getting lots of information from trial outside of clinical positive result-still learning something

Risk and Benefit of P2 Bypassing

Using the (preceded vs ambig+bypass) definition, the positivity and termination rate for trials overall, in the preceded group, and the bypassed group are displayed for all indications in **Table 2**. Chi squared analyses will be conducted in indications where there were at least three trials in both the preceded and bypass group to determine if there was a difference in any of these groups.

There were only enough trials in subgroups reporting the same outcome in AD. Wdae were reported

Table 5, broken down

**Discussion**

MS -overproving efficacy in MS in P2 shouldn’t be running P3, what are the implications for bypass-maybe its good we should do it

Explain why headache is weird for wdae

Nonpositive likely included subgroup analyses that were positive that gave them a different reason to believe in positivity. However these are notoriously x and reviews often advice against this.

Limitations

P2/3s are put into preceded category although unsure if P2 had a clinical positive endpoint-different threshold to move to P3

Some phase2s found sig safety concerns and were terminated but we didn’t capture this

P2/3s letting them be evidence for themselves but don’t really know if they proceeded-especially ones without papers

sometimes no clear primary

only p3 trials that are the first in the indication.

Sometimes p2 had no accessible results- in these cases we called it true bypass because how could it be used to influence p3 trial. But may be same sponsor and hogged the informations.

Some indications may have no clinical or validated surrogate endpoint available (PMS)

Future research

How much of bypass group are made up from modifications of existing approved drugs?

Citation analysis

Not all repourposing drugs

MS does not bypass much and is more likely to be positive- is this the bypass or is that a product of ms drug development

We gave them so much leeway- dose, population, treatment could be diff formulation or diff adjuvant status. The ones that bypass truly bypassed evidence about that treatment in every sense of the word

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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 P3 Trial Sample

Trial records identified from ClinicalTrials.gov (n = 1188)

**Identification**

**Records excluded semi-automatically (n=643):**

• Without an “actual” primary completion date (n=142)

• Non-randomized (n=216)

• Small sample size (n=83)

Trial Status is withdrawn (n=1)

• Primary purpose is diagnostic, screening, or basic science (n=3)

Not testing correct form of treatment (n=55)

• Healthy volunteers included (n=25)

• No US/CAD/EU/Australian enrollment site (n=119)

Duplicates (n=3)

**Screening**

Studies manually assessed for eligibility (n =545)

**Studies excluded manually (n=417):**

• Intervention did not match our criteria (n=52)

• Comparator did not match our criteria (n=16)

• Indication did not match our criteria (n=145)

• No primary efficacy endpoint (n=49)

• Not the first P3 trial in drug/indication pair (n=149)

• Phase 2/3 that did not continue to P3 portion (n=6)

**Included**

Studies included in review (n=126)

**Table 1. Characteristics of the Sample**

|  |  |
| --- | --- |
| Indications | Number of P3 trials  N=126 |
|
|
| All indications |  |
| Alzheimer's disease |  |
| Parkinson's disease |  |
| Amyotrophic lateral sclerosis |  |
| Huntington's disease |  |
| Relapsing Multiple sclerosis |  |
| Progressive Multiple sclerosis |  |
| Headache |  |
| Epilepsy |  |
| TBI |  |
| Stroke |  |
| General |  |
| Large Pharmaceutical funder |  |
| Post-approval status |  |
| Positive primary endpoint |  |
| Terminated for safety or futility |  |
| Phase 3 |  |
| Avg sample size |  |

**Table 2: Prevalence of Bypassing**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Indications | Overall  (N) | Non-Bypass | Bypass | | |
| **Preceded by Positive P2**  **(N, %)** | **Preceded by Ambiguous P2**  **(N, %)** | | **Bypassed P2**  **(N, %)** |
| **Nonpositive** | **Not focused on efficacy** |
| All indications | 126 | 61, 48% | 17, 13% | 17, 13% | 32, 25% |
| Alzheimer's disease | 30 | 7, 23% | 7, 23% | 6, 20% | 10, 33% |
| Parkinson's disease | 14 | 6, 43% | 0, 0% | 4, 29% | 4, 29% |
| Amyotrophic lateral sclerosis | 6 | 3, 50% | 1, 17% | 2, 33% | 0, 0% |
| Huntington's disease | 5 | 1, 20% | 2, 40% | 1, 20% | 1, 20% |
| Relapsing Multiple sclerosis | 19 | 16, 84% | 0, 0% | 0, 0% | 3, 16% |
| Progressive Multiple sclerosis | 4 | 1, 25% | 1, 25% | 1, 25% | 1, 25% |
| Headache | 29 | 22, 76% | 4, 14% | 0, 0% | 3, 10% |
| Epilepsy | 8 | 2, 25% | 1, 13% | 0, 0% | 5, 63% |
| TBI | 5 | 3, 60% | 0, 0% | 1, 20% | 1, 20% |
| Stroke | 6 | 0, 0% | 1, 17% | 1, 17% | 4, 67% |

**Table 3: Overall Positivity and Termination Rate and Bypass**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Non-Bypass | Bypass | | | P-values  non-bypass vs bypass\*\* |
| **Preceded by Positive P2**  **N (%)** | **Preceded by Ambiguous P2**  **N (%)** | | **Bypassed P2**  **N (%)** |
| **Nonpositive** | **Not focused on efficacy** |
| Positivity Rate\* | 36/59 (61) | 4/17 (24) | 3/14 (21) | 13/29 (45) | .004 |
| Termination Rate | 9/62 (15) | 7/17 (41) | 4/15 (27) | 6/32 (19) | .15 |

\*Trials were only included in the positivity analysis if they had primary results available

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

**Table 4. Candidate predictors of bypass**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Candidate Predictors | Overall (N=126)  (N, %) | Type of supporting evidence | | P-values  non-bypass vs bypass\*\* |
| **Non-Bypass**  **N=61**  **(N, %)** | **Bypass**  **N=65**  **(N, %)** |
| Pharmaceutical funder | 109, 87% | 55, 90% | 54, 83% | 0.24 |
| Approved | 97, 77% | 46, 75% | 51, 78% | 0.79 |

**Figure 2: SMD for AD**



**Figure 3: WdAe of indications using subgroup contrasts**

