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, 54 P3 trials (46%) bypassed positive efficacy evidence from a P2 trial. The most common form of bypass was true bypass (19%), where the P3 trial was initiated without a P2 trial investigating the same treatment in the same indication (**see** **Table 2).**

Bypassing and P3 Trial Success

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 (Non-bypass: 57% vs Bypass: 31%, p=0.01). The rate of P3 trial termination due to safety or futility was non-significantly higher in the group that bypassed P2 (Non-bypass: 15% vs Bypass: 29%, 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 (p=0.65) (**see** **Figure 3).**