**Figures and Tables**

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

**Diagram, timeline

Description automatically generated**

**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) |
| 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 P2**  **(N, %)** | **Preceded by Ambiguous P2**  **(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 P2 Bypass and phase 3 trial characteristics / results**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Non-Bypass | Bypass | | | P-values  non-bypass vs bypass1 |
| **Preceded by Positive P2**  **N (%)** | **Preceded by Ambiguous P2**  **N (%)** | | **Full Bypass**  **N (%)** |
| **Nonpositive** | **Not focused on efficacy** |
| 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 |
| Primarily degenerative disease | 21/61 (34) | 11/17 (65) | 13/15 (87) | 8/20 (40) | <0.001 |
| 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 P2 and Full Bypass trials)

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