

Symptomatic Trials for Frontotemporal Dementia

Lessons from the Nabilone-FTD Trial

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BACKGROUND

- ❑ In FTD, pharmacological treatments for neuropsychiatric symptoms (NPS) are based on anecdotal evidence or extrapolation from Alzheimer's studies. There is a strong interest to design symptom-based clinical trials in FTD [1].
- ❑ Agitation is observed in 20-60% of FTD patients, and it is strongly linked to care partner burden, making it a key target [2].
- ❑ One promising drug is nabilone, a synthetic cannabinoid that has shown benefit for agitation in Alzheimer's disease [3].

METHODS

- ❑ In 2021 we obtained an ADDF-AFTD Treat FTD Fund to implement a Canadian-based multisite double-blind randomized cross-over trial of escalating oral nabilone doses with two 6-week treatment periods (NCT05742698).
- ❑ We targeted a sample of 52 FTD subjects, for a 95% power to detect a moderate effect size, factoring a 15% drop-out.
- ❑ To maximize recruitment, we included behavioral and language variants, sporadic and genetic forms, with minimal exclusion criteria.
- ❑ Several assessments were remote to minimize patient burden.

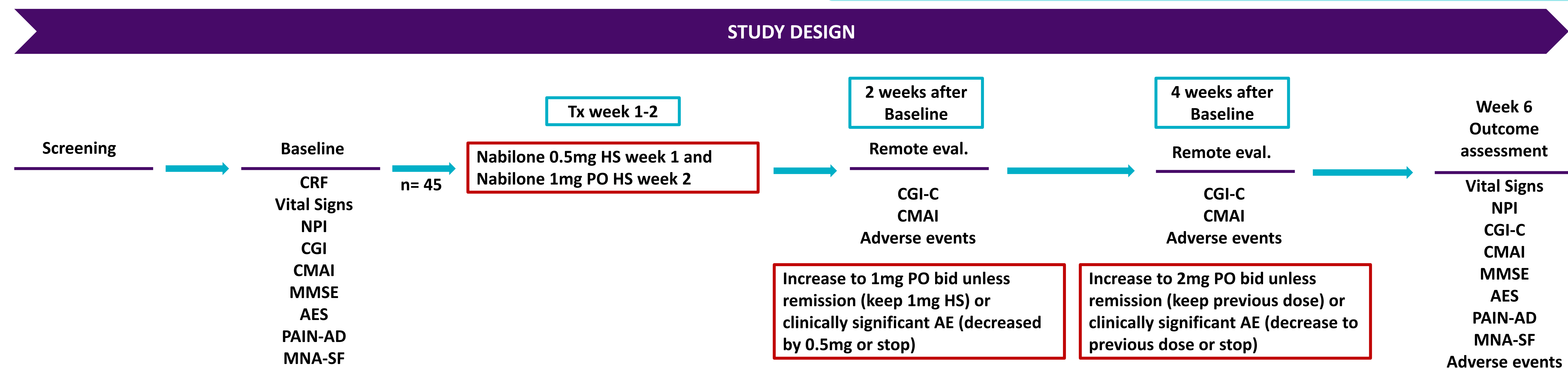


Fig 1. Depiction of one arm of the 6-week treatment phase of the cross-over study. There is a second 6-week treatment phase that is identical after a 2-week washout, but participants receive the other treatment option (placebo or nabilone).

Results

- ❑ Recruitment started in January 2024. Six Canadian sites were progressively activated, which were all academic centers of excellence in FTD.
- ❑ Recruitment lasted a total of 90 months, adding all sites. In this timeframe, only 3 subjects were successfully randomized, corresponding to a recruitment rate of 0.4 patient per site/year.
- ❑ Two subjects prematurely dropped out (one due to deterioration upon change from active to placebo arm, the other due to excessive burden for the family).
- ❑ The overwhelming majority of potential candidates were excluded at pre-screening due to insufficient agitation, prioritizing clinical management over research, and/or lack of perceived benefit from already overwhelmed care partners.
- ❑ The study was terminated in December 2025 after 2 years.

Conclusions

- ❑ Another recent FTD agitation trial failed to reach its target enrolment by a wide margin despite 4 years of recruitment (n=16 versus target of 60) [4].
- ❑ As a rare, heterogeneous, and burdensome disease, FTD poses challenges to traditional trial recruitment and retention. Targeting agitation can be particularly difficult as the symptoms create a heavy burden on care partners and yet may be less common than clinically perceived.
- ❑ Exposure to placebo can also be less tolerated by families, particularly when the prospective treatment is clinically available, or in the second cross-over arm after getting active medication.
- ❑ Future trials should adopt creative study designs such as open-label registries, comparative effectiveness studies, or basket trials with other neurodegenerative diseases.

REFERENCES

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