Background

Essential tremor (ET) is a common movement disorder with a large unmet medical need: 50% of patients report lack of efficacy from first-line therapeutics and one-third (1/3) who respond discontinued due to side-effects. Tremor may be debilitating, impacting patient’s abilities to perform their daily living (ADLs) and occupational demands. It can be a substantial source of social and occupational anxiety, which exacerbates ADLs and/or occupational demands. It can be a substantial discontinuity due to side effects.

Animal and human studies suggest that Cav3 modulators have limited potency, selectivity, and profound side effects. Oral therapeutics are urgently needed by patients whose lives are source of social and occupational anxiety, which exacerbates ADLs and/or occupational demands. It can be a substantial discontinuity due to side effects.

Large unmet medical need: 50% of patients report lack of efficacy from first-line therapeutics and one-third (1/3) who respond discontinued due to side-effects. Tremor may be debilitating, impacting patient’s abilities to perform their daily living (ADLs) and occupational demands. It can be a substantial source of social and occupational anxiety, which exacerbates ADLs and/or occupational demands. It can be a substantial discontinuity due to side effects.

Methods

We reviewed ET studies performed since 2005. We compared published and unpublished clinical data for the Fahn-Tolosa-Marin tremor rating scale (FTM) and the ET Rating Assessment Scale (TETRAS), with emphasis on acceptability, reliability, validity and responsiveness to change. We considered the pros and cons of parallel versus crossover study designs across regulatory, scientific, clinical and operational factors.

Results

While FTM has been widely used in clinical ET studies, it has a ceiling effect for patients with moderate-severe limb tremor - grade 4 tremor is any tremor with amplitude > 4 cm. FTM rates rest tremor, which is uncommon in ET and often misdiagnosed. In contrast, in TETRAS, grade 4 limb tremor is > 20 cm; TETRAS does not rate rest tremor. Upper extremity tremor (a principal concern of most patients) predominates the TETRAS-PS (performance score). TETRAS correlates strongly with FTM, ADL, and transducer measures of tremor, and TETRAS has outstanding inter- and intra-rater reliability, even with untrained raters. Based on repeated measures of 9 ET patients, the minimum detectable change in the TETRAS-PS is 5.5 points. For power analysis, we assumed a change of 8, which corresponds to a mean 44% reduction in amplitude.

A crossover design has operational and sample size benefits, but a parallel design has less dropout risk, reduced total patient weeks, no carryover effect risk, and enhanced treatment blinding. A sample size of 34 subjects was computed at a minimum of 90% power to detect an 8-point reduction in the TETRAS performance subscale, assuming alpha of 0.05.

In prospective sample size computation, using a minimum detectable change (MDC) of 5.5 point change from baseline to end of treatment in the TETRAS-PS subscale when alpha = 0.05 (PASS 2008: One sample t-test – Normal Non-Parametric) 41 subjects are needed in the treatment arm.

Discussion and Conclusions

A double-blind placebo-controlled parallel design with = 34 patients per arm, using the TETRAS-PS as the primary efficacy measure, is optimal for evaluating therapeutics such as CX-8998. When using a discriminating MDC of 5.5 for comparison to placebo, a sample size of 43 subjects per group was selected as a target.

TETRAS-PS possesses critical rating scale characteristics:
- Acceptability
- Reliability
- Responsiveness to change

making it a valid endpoint.

TETRAS-PS:
- Evaluates clinically meaningful activities
- Correlates strongly with ADLs
- Correlates strongly with transducer measures
- Demonstrates strong inter- and intra-rater reliability

Future Work

The above described trial commenced in May 2017. Target recruitment is approximately 92 patient subjects. Performance and characteristics of TETRAS application will be further monitored and evaluated in the study.

References and Notes


*Upper Limb test item includes 0.5 increments.

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