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LOWER SAMPLE SIZE REQUIREMENTS FOR CLINICAL TRIALS STUDYING DIARY SYMPTOMS IN OAB PATIENTS: USE OF THE OVERACTIVE BLADDER SYMPTOM COMPOSITE SCORE FOR SAMPLE SIZE DETERMINATION IN CLINICAL TRIALS

Hypothesis / aims of study

Large efficacy clinical trials can be costly and time consuming. When trials are powered based on efficacy outcomes, use of more sensitive outcomes can reduce the required samples sizes, thus reducing the exposure to patients of experimental products as well as reducing the cost of the studies. The Overactive Bladder Symptom Composite Score (OAB-SCS), which combines 24 hour voiding frequency, urgency severity, and urge urinary incontinence (UUI) episodes, has been shown to discriminate between placebo and pharmacologically treated (trospium chloride) OAB patients. The OAB-SCS may be more sensitive to subtle changes in OAB disease state than individual symptoms alone (e.g., 24 hour frequency, urgency severity/void as measured by the Indevus Urgency Severity Scale©, IUSS©, or frequency of UUI episodes/day), and may offer a valuable alternative to sample size generation in clinical trials.

Study design, materials and methods

Baseline diary data was obtained from a 12-week double-blind, placebo-controlled study demonstrating the effects of trospium chloride vs. placebo in OAB patients. Eligible females and males were 18 years or older with OAB symptoms for at least 6 months, with a minimum urinary frequency of 70 toilet voids per 7 days (i.e., average ≥10 toilet voids per day), and symptoms of urgency as captured in a 7-day diary. All patients were required to have at least 7 urge urinary incontinence (UUI) episodes per week. Patients with incontinence that was predominately stress, insensate, or overflow in nature were excluded from the study, as were those with neurogenic bladder disorders, significant renal disease, uninvestigated hematuria, and urinary tract infection at washout or more than twice during the prior year. Also excluded from the study were patients with: significant bladder outlet obstruction, concurrent anticholinergic drug use or other drug therapy for overactive bladder within 21 days prior to randomization, bladder surgery within 6 months before randomization, cancer, interstitial cystitis, males with prostate-specific antigen (PSA) ≥10 ng/mL, diuretic use, estrogen therapy, and non-pharmacological bladder therapy that were not part of a stable, long-term program. Change from baseline to Week 12 in mean 24 hour frequency, mean UUI/day, mean daily urgency severity/void (as measured by the IUSS), mean volume voided/day, and mean OAB-SCS/day were obtained. Sample sizes required for a new study were then estimated using each of these variables. We assumed, for purposes of this abstract, parametric analysis of variance (ANOVA) for each variable (although some variables may be more appropriately assessed using non-parametric methods). Power was set at 80%, the α-rejection region was set at 0.05, two treatment groups with equal sample sizes were assumed, and an ANOVA with common standard deviations between the treatment groups was assumed. Estimates of variability and treatment effect were obtained from the Phase III pooled studies. SAS® Version 9.1 was used to perform the analysis, and nQuery® Version 5 was used to estimate the sample sizes.

Results

The smallest sample size required to detect a statistically significant treatment effect was found using the volume voided/void parameter (N=66 patients per treatment group) . The second smallest sample size required was found from the OAB-SCS (N=82 patients per treatment group). The largest sample size was found from UUI episodes/day (N=622 patients per treatment group). Table 1 demonstrates the assumed effects sizes (as observed in the Phase III studies) and the required sample sizes to detect statistically significant treatment effect for the diary variables and the OAB-SCS.

Table 1: OAB Parameter LSMean[1] (SE) Baseline, Change from Baseline, and Resulting Sample Size

	Placebo (N=581)		Trospium (N=576)		Sample Size	
	Baseline	Change from Baseline	Baseline	Change from Baseline	Per Group	Total Patients Required
OAB-SCS	36.9 (0.5)	-4.78 (0.4)	36.2 (0.5)	-9.32 (0.4)	82	164
Frequency of Voids/Day	13.1 (0.1)	-1.53 (0.1)	12.8 (0.1)	-2.51 (0.1)	115	230
UUI/Day	4.1 (0.1)	-1.9 (0.1)	3.9 (0.1)	-2.3 (0.1)	622	1244
Daily Urgency Severity/Void	1.76 (0.02)	-0.03 (0.02)	1.77 (0.02)	-0.21 (0.02)	113	226
Volume Voided/Void (mL) (N=573 and 567)[2]	155.4 (2.0)	8.6 (2.1)	155.0 (2.0)	33.9 (2.1)	66	132

1. LSMean – Least Squares Means, SE = Standard Error of LSMean
2. Volume voided/void was not captured for some patients.

Interpretation of results

The OAB-SCS was the second most sensitive OAB measure with respect to detecting a difference between trospium and placebo treatment. The OAB-SCS was more sensitive than either the symptom of 24 hour frequency, UUI/day, or urgency severity per void, and was only slightly less sensitive than the volume voided/void.

Concluding message

Large efficacy clinical trials can be costly and time consuming. When trials are powered based on efficacy outcomes, use of more sensitive variable outcomes can reduce the required samples sizes, thus reducing the exposure to patients of experimental products as well as reducing the cost of the studies. The OAB-SCS, using commonly-accepted patient-reported diary measurements, was demonstrated to be a more sensitive measure of treatment effect differences and thus a more sensitive variable for use in sample size determination and estimation for clinical trials studying OAB treatments.

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