Disclaimer: The following information is fictional and is only intended for the purpose of illustrating key concepts for results data entry in the Protocol Registration and Results System (PRS).

Multiple Period Design Example

(A Phase III Double-Blind Randomized Placebo-Controlled Trial Followed by an Open-Label Period to Assess Vuxcluglyn for Symptom P in Participants with Condition A)

Methods

Study Design

This double-blind (roles blinded: Subjects and Investigators), randomized placebo-controlled interventional study enrolled participants with Condition A from 3 research sites: The Johns Hopkins Hospital (Baltimore, MD, USA), Mount Sinai Hospital (Toronto, Ontario, Canada), and George Eliot Hospital (Nuneaton, England, UK). The protocol and informed consent documents were reviewed and approved by the institutional review boards or ethics committees of the participating institutions. The study was performed in accordance with the Declaration of Helsinki.

After being informed about the study and its potential risks, patients with Condition A were screened for eligibility. The study was conducted in two successive periods. Only enrolled participants who presented at a study site with Symptom P were assigned to the Double-Blind Period. Participants in this period were randomized in a 1:1 ratio to a single dose of Vuxcluglyn, 100 mg capsule, by mouth (PO), or matching placebo capsule. These participants were observed after administration of the intervention. Symptoms were assessed every 30 minutes for 6 hours and then at 12 hours.

During the subsequent, Open Label Period, all enrolled participants were eligible to receive a single dose of Vuxcluglyn, 100 mg capsule, PO, for each episode of Symptom P experienced, whether or not they were assigned to the previous Double-Blind Period. These participants were observed after each administration of Vuxcluglyn, and symptoms were assessed every 30 minutes for 6 hours and then at 12 hours.

Participants

Inclusion Criteria

Participants, regardless of gender, had to be at least 18 years of age and meet the following criteria: diagnosis of Condition A and a stable medical regimen for at least 4 weeks prior to enrollment. In addition, all participants were required to have a sufficient level of education to understand study procedures and be able to communicate with site personnel.

Exclusion Criteria

Participants were excluded from participating in the study for the following reasons: uncontrolled medical disease (e.g., cardiovascular, renal); body mass index < 16.5 kg/m^2; pregnancy and/or lactation; and history of hypersensitivity to Vuxcluglyn or any similar chemical structures.

Assessment of Primary Endpoint

The primary endpoint of this study was the Composite Intervention Outcome Scale (CIOS) at 5 hours following administration of an intervention during the Double-Blind Period. CIOS is a validated, composite measure of response, based on the participant's perception of improvement at assessment. It is composed of 5 items each of which are scored from 0 to 10; the total score is the sum of all five sub-scores with the total possible values ranging from 0 (no improvement) to 50 (complete resolution), with a score ≥ 25 indicating clinically meaningful improvement.

Assessment of Secondary Endpoints

The secondary endpoint in the double-blind period was change from baseline in Symptom Severity Rating (SSR) at 5 hours after administration of an intervention. SSR is a validated, patient-reported measure of symptom severity. SSR values range from 0 (no symptoms) and 5 (severe symptoms).

Other pre-specified endpoints were the Composite Intervention Outcome Scale (CIOS) at 5 hours after administration of each dose of Vuxcluglyn during the Open-Label Period (participants received one dose of Vuxcluglyn for each episode of Symptom P). Participants who did not receive Vuxcluglyn during the Double-Blind Period (because they did not experience Symptom P or received Placebo) were counted in the Open–Label period as "Dose 1". Participants who received Vuxcluglyn in the Double-Blind Period and a second dose in the Open-Label Period were counted as "Dose 2." Thus, "Dose 2" consists of (a) participants who received a dose of Vuxcluglyn during the Double-Blind Period and a second dose during the Open-Label Period; and (b) participants who did not receive Vuxcluglyn during the Double-Blind Period and received two doses of Vuxcluglyn only during the Open-Label Period.

Adverse Event Assessment

Adverse events (AEs) were collected for up to 1 week following the final dose (up to 11 months post-enrollment) by systematic assessment using terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 10.0.

Results

Of the 350 patients screened for eligibility across the 3 study sites, 250 patients with Condition A were enrolled between July 23, 2017 and September 2017 (see Figure 1). The last visit of the final

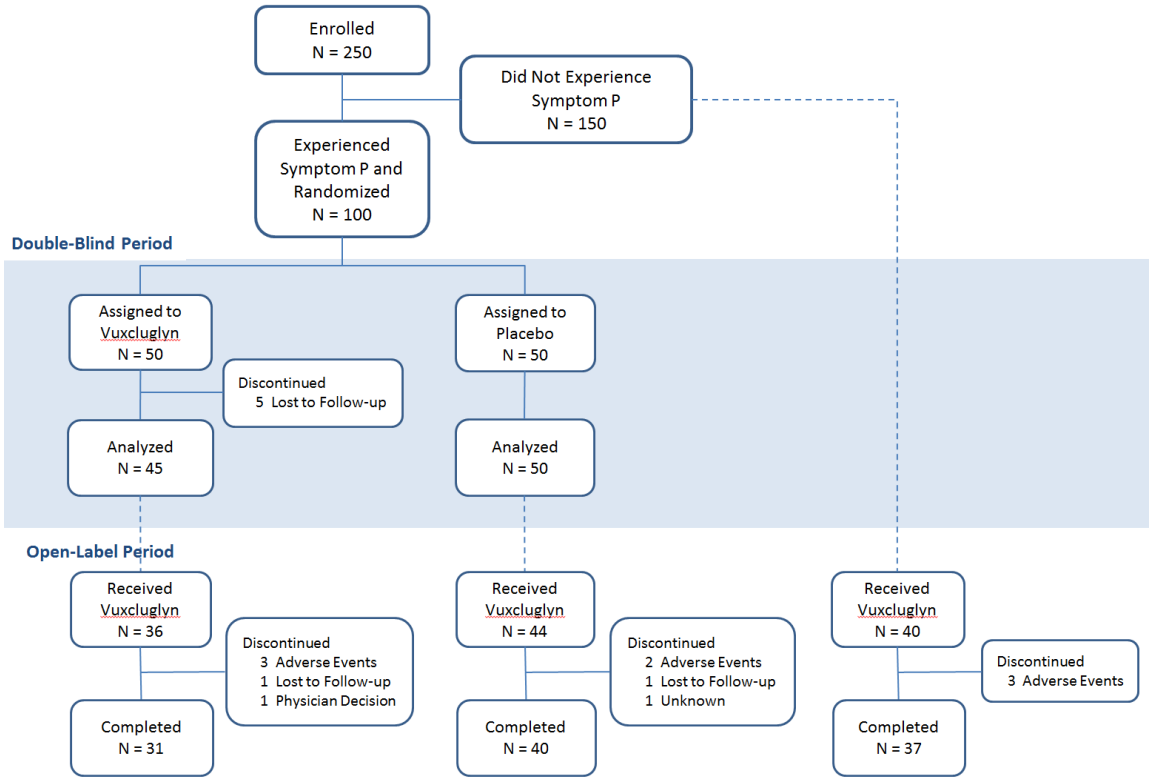

Figure 1. Enrollment, Randomization and Retention of Participants.

participant for the primary endpoint (the Double-Blind Period) was January 25, 2018.The last visit of the final participant for the entire study (the Open-Label Period) was August 20, 2018.

Table 1 lists participant characteristics by randomization group for the Double-Blind Period and for participants who only participated in the Open-Label Period.

Both primary and secondary endpoints for the Double-Blind Period are reported in Table 2. All other pre-specified endpoints for the Open-Label Period are reported in Table 3.

The numbers of participants with adverse events are shown in Table 4.

Table 1. Demographic Characteristics of Participants

Characteristic	Double-Blind Period		Open-Label Period Only	Total
	Vuxcluglyn *n = 50*	Placebo *n = 50*	Vuxcluglyn *n = 40*	*n = 140*
Age in Years *Mean ± SD*	31.7 ± 13.4	32.3 ± 16.4	30.5 ± 14.1	31.6 ± 14.8
Sex – No.				
Male	15	23	18	56
Female	35	27	22	84
Weight - Pounds *Median (range)*	161 (128 – 279)	142 (117 – 311)	156 (99 – 325)	158 (99 – 325)
Race – No.				
White	29	28	22	79
Black	21	22	18	61
Ethnicity – No.				
Hispanic	3	4	2	9
Non-Hispanic	47	46	38	131
Region of Enrollment – No.				
Canada	15	10	12	37
United Kingdom	10	15	12	37
United States	25	25	16	66
SSR Score *Mean ± SD*	3.12 ± 0.61	3.05 ± 0.45	NA	3.09 ± 0.54

SD: Standard Deviation; SSR: Symptom Severity Rating

Table 2. Double-Blind Period Endpoints

Endpoint	Vuxcluglyn, 100 mg *n = 50* *(Mean ± SD)*	Placebo *n = 50* *(Mean ± SD)*	p-Value†
Primary Endpoint			
CIOS at 5h post-dose	33.9 ± 10.2	12.7 ± 5.6	0.004
Secondary Endpoints			
SSR at 5h post-dose	1.17 ± 0.22	1.97 ± 0.36	
SSR change from baseline to 5h	-1.95 ± 0.68	-1.08 ± 0.71	0.044

SD: Standard Deviation; CIOS: Composite Intervention Outcome Scale; SSR: Symptom Severity Rating
† 2 sided, t-test

Table 3. Open-Label Endpoints: Composite Intervention Outcome Scale (CIOS) at 5 hours after Administration of each dose of Vuxcluglyn during the Open-Label Period

CIOS Score	Vuxcluglyn, 100 mg *n = 120* *(Mean ± SD)*
Dose 1 (*n = 84*)	32.21 ± 5.17
Dose 2 (*n = 99*)	42.03 ± 8.25
Dose 3 (*n = 46*)	35.95 ± 4.68
Dose 4 (*n = 26*)	22.44 ± 1.51
Dose 5 (*n = 15*)	18.15 ± 8.98

SD = Standard Deviation

Table 4. Participants with Adverse Events

Adverse Event	Double-Blind Period		Open-Label Period
	Vuxcluglyn *n = 50*	Placebo *n = 50*	Vuxcluglyn *n = 120*
Death	0	0	1
Total Serious*	3	1	2
Total Other	16	8	42
Chest pain	4	3	12
Dizziness	11	5	24
Dyspnea	5	2	9
Hemorrhagic stroke*	1	1	0
Headache	11	8	36
Hyperglycemia	2	0	15
Hypertension	7	1	23
Ischemia	4	2	37
Myocardial infarction*	3	0	2
Palpitations	1	0	13
Ventricular tachycardia	3	2	1

*Adverse event classified as “Serious” (i.e., resulting in death, requiring either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect.)