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

Example Parallel Study Design

(A 24-Week Placebo-Controlled Trial of Remuverol in Adults with Condition A)

Methods

Study Design

This multicenter, placebo-controlled interventional study of Remuverol enrolled participants with Condition A from 3 academic medical centers in Canada, Mexico, and the United States. Participants were recruited based on physician referral between February 2010 and January 2011. Physician-investigators at each center were board-certified in internal medicine, neurology, or rheumatology.

After being informed about the study and potential risks, all participants giving written informed consent underwent a 1-week screening period to determine eligibility for study entry.

At week 0, participants who met the eligibility requirements were randomized in a double-blind manner (subject and investigator) in a 1:1 ratio to Remuverol (15 mg, twice daily) or placebo (twice daily).

The protocol and informed consent documents were reviewed and approved by a recognized ethics review board at each study facility. The study was performed in accordance with the Declaration of Helsinki.

Participants

Inclusion Criteria

Outpatients, regardless of gender, at least 18 years of age and have had Condition A for at least 6 months before the study. Condition A was diagnosed based on medical history and neurological examination. 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 with any cardiovascular, hepatic, or renal conditions that would compromise participation (e.g., hospitalization during the study), in the opinion of the investigator, were excluded. Participants requiring daily use of non-steroidal anti-inflammatory drugs (NSAIDS) or acetaminophen were also excluded. Additional exclusion criteria included history of acute liver injury (e.g., hepatitis) or severe cirrhosis; Body Mass Index (BMI) of >40 kg/m^2; pregnancy or breast-feeding; and daily use of narcotics.

Study Objectives

The primary objective was to evaluate the efficacy of Remuverol 15 mg twice daily compared to placebo in reducing mean pain from baseline as measured by the 11-point Short Pain Scale (SPS-11) 24-hour pain ratings at the end of the 24-week double-blind study period.

Secondary objectives included determining the Response Rate using different criteria and time point combinations: (1) number of responders with a 50 percent or greater reduction in pain as determined by SPS-11 at week 12; (2) number of responders with a 50 percent or greater reduction in SPS-11 pain at week 24; and (3) number of responders with a 75 percent or greater reduction in SPS-11 pain at week 24.

Adverse events were also assessed.

Assessment of Primary Outcome Measure

SPS-11 is a validated, self-reported instrument. The severity of pain scores on the SPS-11 range from 0 (no pain) to 10 (worst possible pain). Subjects were administered the SPS-11 during visit 1 (week 0; baseline) and at week 24 as an

assessment of pain intensity over the past 24-hour period. The average change from baseline in SPS-11 at week 24 was determined.

Assessment of Secondary Outcome Measures

The response rate was defined as the number of participants with a ≥50% or ≥75% reduction in SPS-11 pain score from baseline to endpoint (last observation carried forward). The ≥50% response rate was assessed at weeks 12 and 24; and, the ≥75% response rate was assessed at week 24.

Adverse Event Assessment

Adverse events (AEs) were collected by systematic assessment using terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0.

Statistical Analyses

The analysis of the primary endpoint was performed on the intention to treat (ITT) population. Other endpoints were assessed based on the per-protocol population with data available at each relevant time point. Treatment effects were assessed using a 2-sided significance level of 0.05. All analyses were performed using SAS software (version 12.8; SAS Institute, Cary NC).

It was calculated for this study that, approximately 200 participants randomized in a 1:1 fashion between the 2 arms would have at least 85% power to detect a difference of 0.56 points in mean SPS-11 pain score between Remuverol and placebo from baseline to week 24. Sample size was determined using a 2-sided 2-sample *t* test ($\alpha = 0.05$). Assumptions included a common standard deviation of 1.14 and a discontinuation rate of 7%.

Table 1. Baseline Demographics and Disease Characteristics of Participants

CHARACTERISTIC	REMUVEROL N = 101	PLACEBO N = 99	TOTAL N = 200
Age, years, mean (SD)	34.78 (9.72)	35.34 (10.71)	34.98 (9.89)
Sex, n (%)			
Female	60 (59.4)	63 (63.6)	123 (61.5)
Ethnicity, n (%)			
African	5 (4.95)	4 (4.04)	9 (4.50)
Caucasian	90 (89.11)	90 (90.91)	180 (90.00)
Hispanic	5 (4.95)	4 (4.04)	9 (4.50)
Native American	1 (0.99)	1 (1.01)	2 (1.00)
Region of Enrollment, n (%)			
United States	44 (43.56)	47 (47.48)	91 (45.50)
Canada	35 (34.65)	35 (35.35)	70 (35.00)
Mexico	22 (21.78)	17 (17.17)	39 (19.50)
QTF Classification of Spinal Disorder*			
Class 0, n (%) – *no pain*	16 (15.84)	14 (14.14)	30 (15.00)
Class 1, n (%) – *pain without radiation*	73 (72.28)	68 (68.69)	141 (70.50)
Class 2, n (%) - *pain with proximal extremity radiation*	12 (11.88)	17 (17.17)	29 (14.50)
Body Mass Index (BMI), kg/m2, mean (SD)	26.65 (4.50)	27.41 (4.72)	26.91 (4.55)
Short Pain Scale (SPS-11) Score, mean (SD)	6.48 (1.34)	6.57 (1.73)	6.52 (1.61)
Duration of Condition A, years, mean (SD)	3.82 (3.18)	3.47 (2.95)	3.75 (3.06)
Height, cm, mean (SD)	186.42 (9.46)	176.91 (8.28)	181.33 (8.95)
Weight, kg, mean (SD)	77.03 (14.38)	78.53 (13.56)	77.98 (13.79)

*Quebec Task Force (QTF) Classification of Spinal Disorders consists of 8 classes ranging from 0 (no pain) to Class 7 (spinal stenosis).

Results

Disposition of Participants

Of the 200 participants enrolled between March and December 2010, 51% (N = 101) were randomized to Remuverol and 49% to placebo (N = 99). (*see* Table 1) Of those randomized to Remuverol, 79% (N = 80) completed the study and of those randomized to placebo 82% (N = 81) completed the study (*see* Figure 1). The last visit for the final participant for assessment of the primary and secondary outcomes was in August 2011.

There was not a statistically significant difference in overall discontinuation rates. More participants discontinued due to adverse events (*P* = 0.01) in the Remuverol Arm (10%) than the Placebo Arm (8%).

Efficacy Outcomes

Primary Outcome

Participants in the Remuverol Arm showed a greater reduction in pain than participants in the placebo arm (P = 0.002; Mixed Model Analysis) as measured by the change in SPS-11 pain score at week 24 compared to baseline (*see* Table 2).

Secondary Outcomes

All secondary outcome data are in Table 3. At the 50% SPS-11 pain reduction threshold, participants responded significantly better on Remuverol than placebo (p = 0.008) at week 24, but not at week 12 (p = 0.352). And, at the 75% threshold, participants also responded significantly better on Remuverol than placebo at week 24 (p = 0.006).

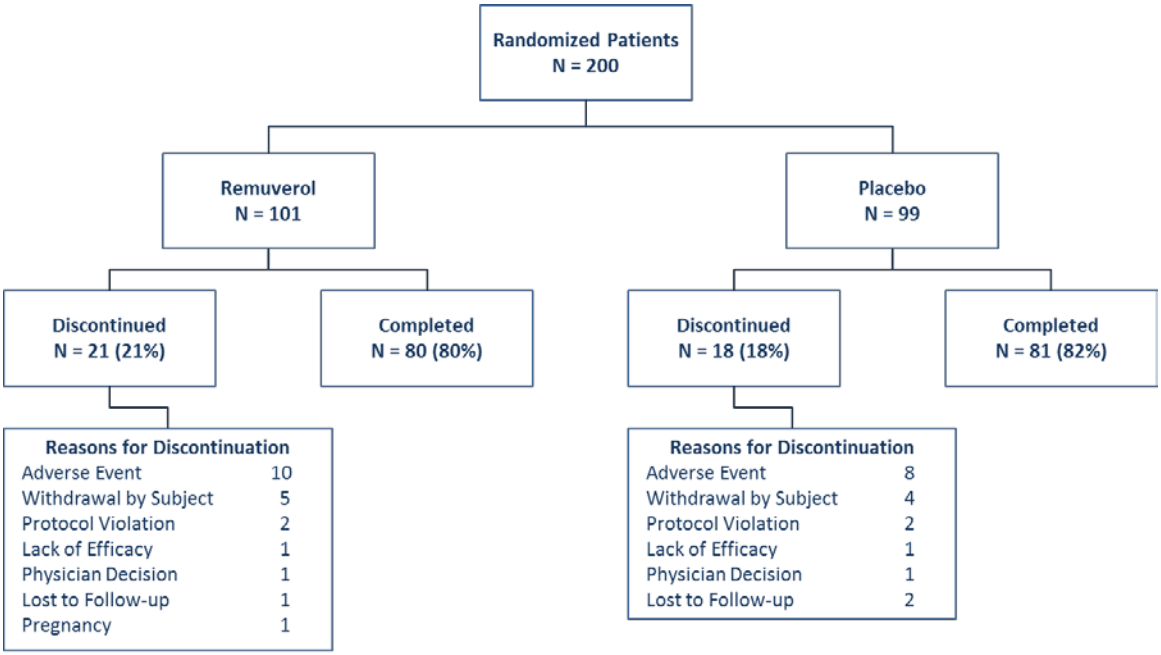

Figure 1. Enrollment, Randomization, and Retention of the Study Participants.

Table 2: Mean Change from Baseline to Week 24 in SPS-11 24-Hour Pain Score of Participants with Condition A

	Remuverol		Placebo		
Measure	N	Mean Change (SE)	N	Mean Change (SE)	P Value*
Change in SPS-11 Score: Baseline to Week 24	101	-3.84 ± 0.61	99	-2.08 ± 0.51	0.002

* Mixed Models Analysis

Table 3: SPS-11 Pain Response Rates from Baseline to Endpoint in Patients with Condition A

Response Rate at 50% Reduction in SPS-11 Pain					
	Remuverol		Placebo		
Time Frame	N	No. Respondents	N	No. Respondents	P Value*
Week 12	98	45	95	41	0.352
Week 24	76	73	81	52	0.008
Response Rate at 75% Reduction in SPS-11 Pain					
Week 24	76	57	81	32	0.006

* Fisher Exact

Adverse Events

There were no deaths during this study. Although no serious adverse events (SAEs) were reported in participants in the Placebo Arm (N = 99), 4 SAEs were reported in 4 participants in the Remuverol Arm (N = 101):

- Anemia iron deficiency,
- Viral meningitis,
- Psoriasis, and
- Idiopathic thrombocytopenic purpura.

Of other adverse events (AE) that were not SAEs and reported in over 1% of participants at risk in at least one arm, 98 participants in the Remuverol Arm (N = 101) and 46 participants in the Placebo Arm (N = 99) experienced at least one AE (*see* Figure 2).

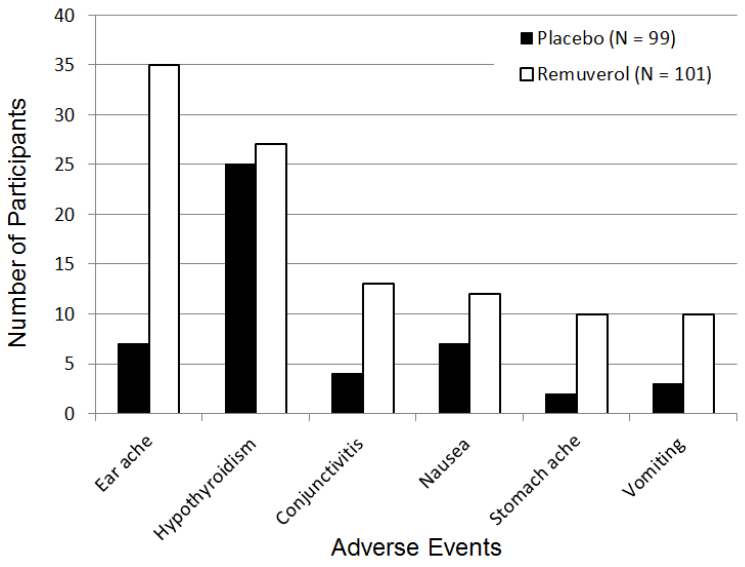

Figure 2. Six most common non-serious adverse events in >1% of participants treated with Remuverol or placebo