Samelisant (SUVN-G3031) Demonstrates Significant Reduction in Excessive Daytime Sleepiness In Patients with Narcolepsy: Phase-2 Results

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Introduction:

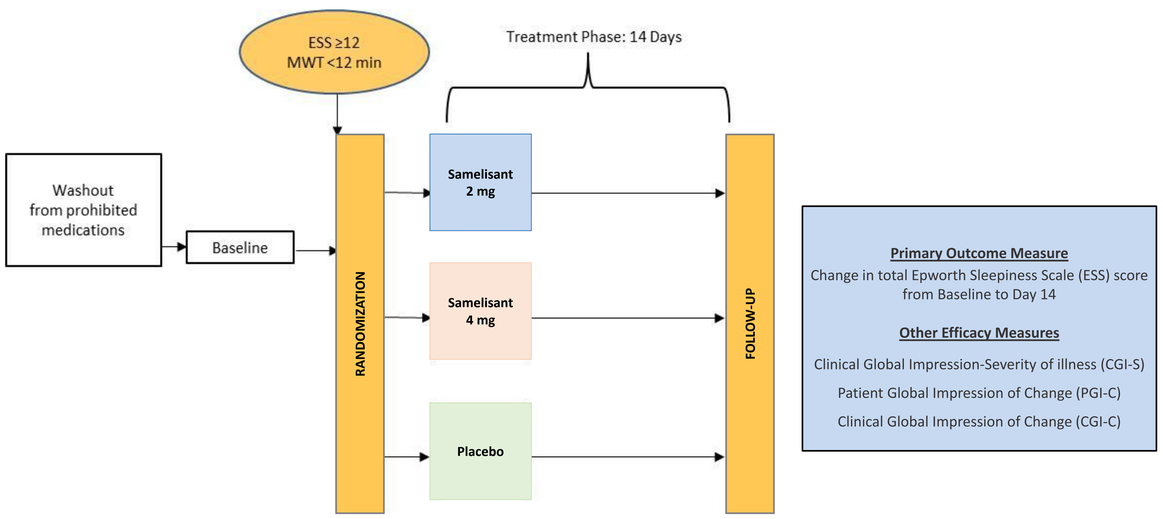
Narcolepsy is a chronic neurological sleep disorder marked by excessive daytime sleepiness (EDS), sudden sleep attacks, cataplexy, hypnagogic hallucinations, and sleep paralysis. Existing therapies often present challenges, including side effects, limited efficacy, and need for complex combination regimens. Samelisant, a selective histamine-3 receptor inverse agonist, is a promising therapeutic option. In diverse animal models, Samelisant promoted wakefulness and reduced cataplexy, supporting its potential benefit in narcolepsy. Samelisant's safety/tolerability have been established in healthy humans. Efficacy and safety of Samelisant was evaluated in narcolepsy patients with moderate to severe EDS (NCT04072380).

Objective:

To evaluate the efficacy and safety of Samelisant for treatment of EDS in narcolepsy patients.

Methods:

Fig 1. Phase-2 Study Design



After a screening period of up to 4 weeks, treatment of 2 weeks followed by safety evaluation after 2 weeks.

Key Inclusion Criteria:

- Must be between the ages of 18 to 65 years, inclusive.
- Must have a body mass index ranging from 18 to <45 kg/m^2.
- Have narcolepsy with or without cataplexy (NT1 or NT2) based on the International Classification of Sleep Disorders (3rd Edition) criteria for the diagnosis of narcolepsy.
- Have an ESS total score of ≥12 and MWT time of <12 minutes at Baseline visit.

Key Exclusion Criteria:

- Habitual wake-up time after 8 AM as assessed by sleep diary, habitual sleep time of <6 h and habitual bedtime past 1 AM as determined by sleep diary entries.
- Use of any investigational therapy within the 30-day period.
- Nicotine dependence that has an effect on sleep (e.g., a patient who routinely awakens at night to smoke).
- Use of concurrent medications prescribed to treat narcolepsy or any indication as specified including stimulants, antidepressants and sodium oxybate before Baseline visit.

Results:

Table 1. Demographic and Baseline Characteristics

Characteristic	Placebo (N=57)	Samelisant 2 mg (N=54)	Samelisant 4 mg (N=53)
Age	32.9 (10.07)	29.5 (8.51)	34.6 (9.71)
Body Mass Index (kg/m^2)	29.35 (6.062)	29.41 (6.391)	27.89 (5.587)
Male [n (%)]	16 (28.1)	16 (29.6)	16 (30.2)
Race [n (%)]			
White	39 (68.4)	39 (72.2)	34 (64.2)
Black or African American	14 (24.6)	12 (22.2)	13 (24.5)
Other	4 (7.0)	3 (5.6)	6 (11.3)
Ethnicity [n (%)]			
Hispanic or Latino	6 (10.5)	4 (7.4)	9 (17.0)
NT1 (With Cataplexy) [n (%)]	32 (56.1)	27 (50.0)	27 (50.9)

Fig 2. Least Squares Mean Change from Baseline in ESS Total Score

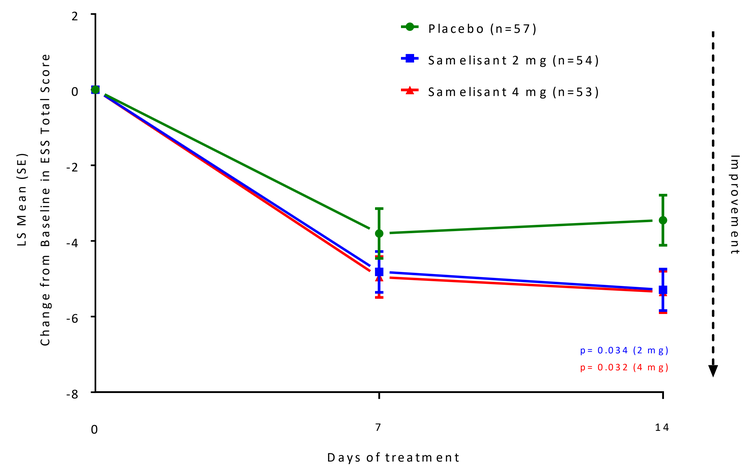


Table 2. Summary of Efficacy Outcomes

Efficacy Endpoints	N	Baseline Score, Mean (SD)	Change from Baseline at Day 14 or Day 14, Mean (SD)	Treatment Difference at Day 14 Versus Placebo: Mean Difference	Maximum Likelihood Estimate Difference (95% CI)	p-value (MMRM Analysis)
Primary Efficacy Endpoint						
ESS						
Placebo	57	17.1 (2.99)	-3.3 (4.61)	-	-	-
Samelisant 2 mg	54	17.4 (2.77)	-5.1 (5.00)	-1.8	-1.822 (-3.506, -0.139)	**0.034**
Samelisant 4 mg	53	17.6 (2.83)	-5.6 (5.46)	-2.3	-1.853 (-3.551, -0.155)	**0.032**
Secondary Efficacy Endpoint						
CGI-S						
Placebo	55	4.8 (0.79)	-0.8 (1.17)	-	-	-
Samelisant 2 mg	54	4.7 (0.77)	-1.2 (1.24)	-0.4	-0.415 (-0.781, -0.049)	**0.026**
Samelisant 4 mg	52	4.9 (0.82)	-1.4 (1.19)	-0.6	-0.503 (-0.870, -0.136)	**0.007**
Exploratory Efficacy Endpoints						
PGI-C						
Placebo	54	4.8 (0.99)	3.7 (1.12)	-	-	-
Samelisant 2 mg	53	4.6 (0.95)	3.2 (1.16)	-0.54	-0.599 (-1.005, -0.192)	**0.004**
Samelisant 4 mg	51	4.7 (1.03)	2.8 (1.10)	-0.86	-0.835 (-1.244, -0.425)	**<0.0001**
CGI-C						
Placebo	57	-	3.5 (0.91)	-	-	-
Samelisant 2 mg	54	-	2.8 (1.01)	-0.70	-0.710 (-1.042, -0.379)	**<0.0001**
Samelisant 4 mg	53	-	2.6 (0.92)	-0.90	-0.797 (-1.129, -0.464)	**<0.0001**

Table 3. Summary of Sleep Diary Parameters (Post-hoc)

	N	Baseline Score Mean (SD)	Change From Baseline at Day 14 Mean (SD)	Difference from Placebo	p-value
Sleep Parameters					
Total No. of Arousals					
Placebo	57	91.4 (37.34)	-1.4 (29.01)	-	-
Samelisant 2 mg	54	96.3 (46.86)	-20.5 (31.11)	-19.1	**0.0941**
Samelisant 4 mg	53	101.9 (52.62)	-23.6 (44.96)	-22.2	**0.0272**
Next Day Alertness					
Placebo	57	5.8 (1.68)	0.7 (1.10)		-
Samelisant 2 mg	54	5.9 (1.60)	0.8 (1.30)	0.1	**0.1468**
Samelisant 4 mg	53	5.5 (1.56)	0.8 (1.08)	0.1	**0.0569**
NAP Duration (min)					
Placebo	57	60.2 (40.19)	9.4 (36.78)	-	-
Samelisant 2 mg	54	77.5 (49.66)	-13.3 (43.82)	-22.7	**0.1106**
Samelisant 4 mg	53	74.1 (41.16)	-15.7 (42.81)	-25.1	**0.0388**

Conclusions:

- Samelisant as a monotherapy met the primary endpoint with significant reduction in EDS.
- Samelisant was generally safe and well tolerated in narcolepsy patients.
- A global Phase-3 (AWAKE) study for the treatment of narcolepsy is in progress in United States, Canada, France, Germany, Italy and Spain.