Introduction

Eric Bastings, MD
Acting Director
Division of Neurology Products

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

Tasimelteon

November 14, 2013

Tasimelteon

- Melatonin agonist
- Proposed for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in the totally blind

Non-24

- Non-24 is a type of circadian rhythm sleep disorder that occurs in totally blind individuals due to loss of the normal input from the eyes about environmental light levels
- Cyclical daytime sleepiness and nighttime insomnia

Pivotal Studies

- Two placebo-controlled trials, study 3201 (SET) and study 3203 (RESET)
- Agreement on primary endpoint could not be reached with the sponsor
  - Sponsor proposed a primary endpoint of entrainment of the circadian melatonin rhythm as measured by the urinary metabolite of melatonin, aMT6s

Pivotal Studies

- FDA did not accept biomarker based endpoint because clinical benefit from entrainment in Non-24 would occur in a reasonably brief period of time, and would be readily measurable
- FDA asked sponsor to propose a primary endpoint capable of demonstrating a *clinical* benefit from tasimelteon, but sponsor maintained biomarker-based primary endpoint

Clinical Endpoints

- Agreement that endpoint(s) that focused on sleep on the days when symptoms were worst would have the greatest likelihood of identifying a beneficial effect
  - e.g., Lower Quartile of Nighttime Total Sleep Time and Upper Quartile of Daytime Total Sleep Duration
- These endpoints were considered as secondary by the sponsor, but would have been acceptable primary endpoints for FDA

Efficacy Results

- Both studies positive based on applicants pre-specified primary analyses (but biomarker-based)
- Secondary endpoints directly assessing clinical benefits positive, but not ordered to correct for type 1 error related to multiple comparisons

Efficacy

1) No drugs are currently FDA approved for Non-24 Hour Sleep-Wake Disorder (Non-24). Please discuss the appropriateness of Non-24 as an indication for FDA approval of drug therapies.

a. **DISCUSSION:** Are the intended population and diagnostic criteria reasonable?

b. **DISCUSSION:** Are there any other concerns with the way the condition is defined or represented?

c. **DISCUSSION:** Are you satisfied that Non-24 is a bona fide sleep disorder with consequences for patients?

d. **VOTE:** Is Non-24 appropriate as an indication for an FDA-approved drug therapy?

2) The clinical endpoints used in the efficacy studies supporting the new drug application (NDA) for tasimelteon in Non-24 are novel, and have not been used to support the approval of other drugs.

a. **DISCUSSION:** Please discuss the appropriateness of the clinical endpoints (those that sought to measure directly how patients feel or function), specifically, Lower Quartile of Nighttime Total Sleep Time (LQ-nTST), Upper Quartile of Daytime Total Sleep Duration (UQ-dTSD), and Clinical Global Impression of Change (CGI-C).

b. **VOTE:** Are the clinical endpoints used in the tasimelteon development program appropriate to support an indication in Non-24?

3) Please discuss the evidence of efficacy presented.

a. **DISCUSSION:** Are there any concerns with the design, conduct or analysis of the efficacy trials?

b. **VOTE:** Has substantial evidence of efficacy been presented for tasimelteon in Non-24?

Safety

4) **DISCUSSION:** Please discuss the safety evidence presented for tasimelteon.

5) **VOTE:** Has the safety of tasimelteon in Non-24 been adequately addressed?

NDA 205677
Tasimelteon Efficacy and Safety

Peripheral and Central Nervous System Drugs Advisory Committee
November 14, 2013

Devanand Jillapalli, MD
Medical Officer
Division of Neurology Products
Center for Drug Evaluation and Research

Clinical Benefit

- Clinical benefit for approval is demonstrated by endpoints that are clinically meaningful:
  - Clinical endpoints that directly assess "prolonged life, improved physical condition, or reduced pain" (US v Rutherford, 1977). *Established* surrogate endpoints (e.g., blood pressure) can be used in lieu of clinical outcomes.
- Accelerated approval (Subpart H): Surrogate endpoint reasonably likely to predict *clinical benefit*.

Surrogate and Clinical Endpoints

- Surrogate endpoints *do not directly* assess clinical benefit:
  - May be used to describe the condition.
  - May be correlated to effects on clinical endpoints.
  - Used in clinical trials to ***predict*** clinical benefit (Subpart H).
- Clinical endpoints *directly* measure clinical benefit:
  - Primary clinical endpoint shows clinical benefit and defines success of the trial.
  - Such clinical benefit can be described in labeling to enable healthcare providers and patients to assess benefit versus risk.

Regulatory History

- Multiple interactions with the Applicant (7/9/12, 10/10/12, 11/28/12): No agreement on primary endpoint.
- 12/10/12: Telecon between the Agency and the Applicant. No agreement on the primary endpoint.
- 12/11/12: Statistical analysis plan finalized.
- 12/12/12: Study 3201 database lock and unblinding.

Disagreement on Primary Endpoint

- Applicant proposed primary endpoint:
  - Nighttime Total Sleep Time (nTST): used in insomnia studies.
  - Entrainment of circadian melatonin rhythm as measured by urinary metabolite of melatonin: does not directly measure clinical benefit.
- Agency asked for clinical primary endpoint to directly assess *clinical benefit*. Existing body of knowledge about circadian rhythms suggested:
  - Clinical benefit in Non-24 Hour Disorder could occur in reasonable time-frame.
  - Clinical endpoints could readily measure benefit on nighttime and daytime sleep.

Prior Agreement on Clinical Endpoints

- Agreement between the Applicant and the Agency during early drug development that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit.
  - Lower Quartile of Nighttime Total Sleep Time (LQ-nTST).
    - Correlates with the most symptomatic phase of circadian cycle (maximum misalignment).
    - Lower Quartile of nTST data has less variability than nTST.
  - Upper Quartile of Daytime Total Sleep Duration (UQ-dTSD).
- LQ-nTST or UQ-dTSD, while agreed upon, were not ordered in the trials.

FDA's Statistical Analyses of Clinical Endpoints

Two Efficacy Issues

- Lack of agreement on primary endpoint.
- The effect of tasimelteon on the periodic nature of nighttime and daytime symptoms of Non-24 Hour Disorder.
  - Periodicity of symptoms – a key feature of Non-24 Hour Disorder.
  - Differentiates from a non-specific soporific effect.

Efficacy Issue 1

- Lack of agreement on primary endpoint.

Lack of Agreement on Primary Endpoint

- Study 3201 and Study 3203 were both positive based on Applicant's pre-specified analyses.
- Question: Was clinical benefit shown?
- Pre-specified primary endpoint of entrainment rate in Study 3201 (non-entrainment rate in Study 3203) was positive.
  - Entrainment does not directly measure clinical benefit.
  - Did patients receive any benefit?

Lack of Agreement on Primary Endpoint

- Step-down primary endpoint in Study 3201 : entrainment rate ***and*** N24CRS score ≥ 3.
  - N24CRS is composed of LQ-nTST, UQ-dTSD, Clinical Global Impression-Change (CGI-C) and Midpoint of Sleep Timing (MoST).
  - Clinical meaningfulness of MoST is uncertain.
  - A primary endpoint does not have to measure every aspect of the condition to define success of the trial.

Assessment	Threshold of response
LQ-nTST	≥45 minutes increase in average nighttime sleep duration
UQ-dTSD	≥45 minutes decrease in average daytime sleep duration
MoST	≥30 minutes increase and a standard deviation ≤2 hours during double-masked phase
CGI-C	≤2.0 from the average of D112 and Day 183 compared to baseline

Source: Applicant's submission; Sequence 000: Module 2.7.4, ISE: Table 3, page 21.

Lack of Agreement on Primary Endpoint

- Pre-specified step-down primary endpoint was positive in Study 3201.
- Question: Did N24CRS show clinical benefit?
- N24CRS – a composite endpoint: Need know the fractional contribution to the positive effect on the step-down primary by its individual components that directly assess clinical benefit.

Lack of Agreement on Primary Endpoint

- Individual components of Step-down primary – LQ-nTST, UQ-dTSD and CGI-C, directly assess clinical benefit, and strongly suggest overall clinical benefit. However, there are caveats.
  - Step-down primary also contained components that do not directly assess benefit (entrainment and MoST). Unclear how much these components contributed to the overall effect.
  - 12 subjects were excluded from analysis (8 placebo versus 4 tasimelteon): potential for introducing bias.

Lack of Agreement on Primary Endpoint

- Caveats limit conclusion that step-down primary endpoint showed clinical benefit. But, there is strong suggestion of benefit.
- Need to look at secondary clinical endpoints (not ordered), LQ-nTST and UQ-dTSD, and CGI-C, to establish clinical benefit, but raises potential for inflation of type 1 error.

Secondary Clinical Endpoints and Corresponding p-values in Study 3201 and Study 3203

Clinical Endpoints	Study 3201 N = 84 p-value	Study 3203 N = 20 p-value
LQ-nTST (hours)	0.052	0.023
UQ-dTSD (hours)	0.011	0.007
CGIC[1]	0.008	NA
nTST (hours)	0.117	0.153
dTSD (hours)	0.015	0.022

[1]For CGIC, n=71 since CGIC was missing for 13 patients; NA = Not assessed in Study 3203.

P-values based on permutation ANCOVA analyses without site.

Source: Dr. Jingyu Luan's analyses.

Lack of Agreement on Primary Endpoint

Secondary endpoints – LQ-nTST and UQ-dTSD, and CGI-C, were not ordered. Inflation of Type 1 error issue considered by clinical team.

- Most important clinical endpoints were all positive.
- **Independent substantiation**: greatly reduces the potential that clinical benefit was a chance finding or there were undetected biases.

•Conclusion of the clinical team: Clinical benefit for tasimelteon has been independently substantiated in two clinical studies.

Efficacy Issue 2

The effect of tasimelteon on the periodic nature of nighttime and daytime symptoms of Non-24 Hour Disorder.

Effect on Periodicity

- Symptoms in Non-24 Hour Disorder are periodic in nature.
- An effect on periodic nature of symptoms important to support clinical benefit in Non-24 Hour Disorder, i.e., differentiate from an ordinary soporific effect.
- LQ-nTST was used because it is thought to reflect the worst nights (most symptomatic) that are expected to occur periodically.

Effect on Periodicity

- Another approach: look at the entire sleep dairy for an effect on stabilization of periodic nighttime and daytime symptoms.
- Post-randomization, night/day sleep data collected for 6 months or 2 circadian cycles, whichever was less.
- Absolute difference between In-Phase (asymptomatic time) and Out-of-Phase (most symptomatic time) in a cycle for a given individual. Treatment group means were compared.

Absolute Value of the Difference for In-Phase and Out-of-Phase in Patients with ≥ 70% of One Cycle Post-randomization

Total Sleep Duration at night

Cycle (N)	Placebo (Hour)	Tasimelteon (Hour)	Diff (Hour)	P-Value[a]	Permutation P-Value[b]
Cycle 1 (N= Placebo: 38; tasimelteon: 39)	1.42	0.53	0.89	0.0007	0.0004
Cycle 2 (N= Placebo: 33; tasimelteon: 37)	1.00	0.52	0.49	0.0105	0.0087
Cycle 1+2 (N= Placebo: 38; tasimelteon: 39)	1.15	0.43	0.72	0.0004	0.0003

Total Sleep Duration during day

Cycle (N)	Placebo (Hour)	Tasimelteon (Hour)	Diff (Hour)	P-Value[a]	Permutation P-Value[b]
Cycle 1 (N= Placebo: 38; tasimelteon: 39)	0.97	0.39	0.58	0.0149	0.0100
Cycle 2 (N= Placebo: 33; tasimelteon: 37)	0.64	0.29	0.35	0.0181	0.0151
Cycle 1+2 (N= Placebo: 38; tasimelteon: 39)	0.73	0.30	0.43	0.0181	0.0148

[a] P-value was based on analysis of variance model.
[b] P-value was based on the permutation ANOVA t-test

Source: Applicant's analyses; Sequence 028: Tables 1 & 2, page 2.

Effect on Periodicity

- Statistically significant effect favoring tasimelteon on the absolute value of the difference between In-phase and Out-of-Phase for Cycle 1 and 2 post-randomization, indicates an effect of tasimelteon on the periodic nature of Non-24 Hour Disorder.

Efficacy Conclusion

- The clinical benefit for tasimelteon has been independently substantiated in two adequate and well-controlled clinical studies.
- There is substantial evidence of effectiveness for tasimelteon in the treatment of Non-24 Hour Disorder.

Safety

Safety

- No major safety issues identified with regard to:
  - serious adverse events, and adverse events leading to early withdrawal from trial
  - potential for drug-induced liver injury
  - metabolic/endocrine laboratory parameters
  - potential for adverse effect on cardiac repolarization
  - adverse effect on vital signs
  - potential for suicide
  - adverse effects due to abrupt withdrawal

Common Adverse Events in Subjects with Non-24 Hour Disorder

Adverse event	Tasimelteon N=52		Placebo N=52	
	n	%	n	%
At least one TEAE	40	76.9	28	53.9
Headache	8	15.4	3	5.8
Alanine aminotransferase increased	5	9.6	2	3.9
Nightmare/abnormal dreams	4	7.7	0	0
Conduction disorder	3	5.8	0	0
Sleep disorder	3	5.8	0	0
Upper respiratory tract infection	3	5.8	0	0
Somnolence	3	5.8	1	1.9
Urinary tract infection	3	5.8	1	1.9

Common, defined as experienced by at least 3 subjects in the tasimelteon group and with a ≥ 2-fold greater frequency than in placebo group (ranked by frequency in the tasimelteon group).

Source: Reviewer's analysis of relevant datasets.

Overall Conclusion

The clinical benefit of tasimelteon outweighs its risks in subjects with Non-24 Hour Disorder.

NDA 205-677 Tasimelteon Efficacy Analysis

Peripheral and Central Nervous System Drugs Advisory Committee

November 14, 2013

Jingyu (Julia) Luan, Ph.D.

Outline

- **Background:**
  - **summary of important events related to statistical analysis**
- **Statistical Reviewer's Efficacy Analysis**
- **Summary**

Study 3201 Important Events	Date	Primary Endpoint	Sample Size	Note
Original	5/24/2010	nTST	160	mean=39 mins std=66 mins
First Patient Enrolled	8/25/2010			
Amendment 6	8/8/2011	nTST	100	mean=30 mins std=45 mins
Amendment 9	5/21/2012	Entrainment	84	80/84 patients (95%) randomized; 47/84 patients (56%) completed
Last Patient Completed	10/29/2012			
Amendment 11	12/11/2012	Entrainment	84	
Data Unblinding	12/12/2012	Entrainment	84	

Caveat

- **No Agreement**: between the sponsor and the Agency regarding primary endpoint, analysis population and analysis method

- **Agency's Decision**: efficacy evaluation should be based on clinical endpoints

- **Reviewer's Analysis**: post-hoc exploratory analysis w/o multiplicity adjustment

Study	Issues	Sponsor's Position	Agency's Position
3201 (SET)	Primary Endpoint	Entrainment Clinical Response Rate	LQ-nTST, UQ-dTSD, CGI-C, nTST, dTSD
	Analysis Population	Randomized population (n=84) Sponsor ITT (n=78) Sponsor Analysis Population (n=72)	ITT (n=84) (all the 84 randomized patients should be included in the ITT for this study)
	Analysis Method	ANCOVA with site as a factor	Permutation ANCOVA w/o site
3203 (RESET)	Primary Endpoint	Non-entrainment	LQ-nTST, UQ-dTSD, CGI-C, nTST, dTSD
	Analysis Method	ANCOVA w/o site as a factor	Permutation ANCOVA w/o site

Reviewer's Analysis

- **Histograms for each clinical endpoint in each study**
  - **LQ-nTST, UQ-dTSD, CGI-C, nTST and dTSD**

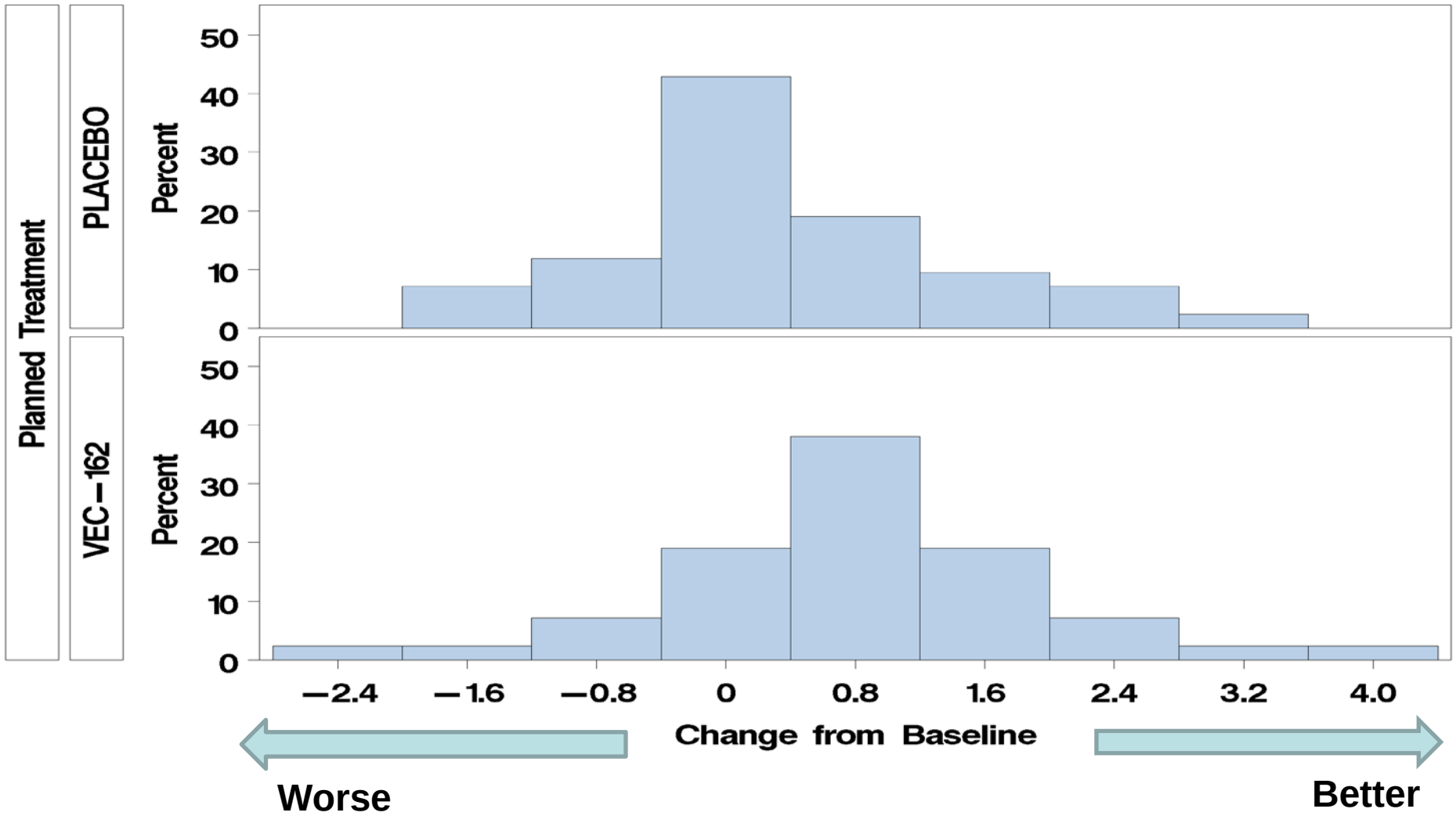
  (The clinical endpoints are likely correlated with each other.)

- **Description of the 12 patients excluded from the Randomized Population by the sponsor**

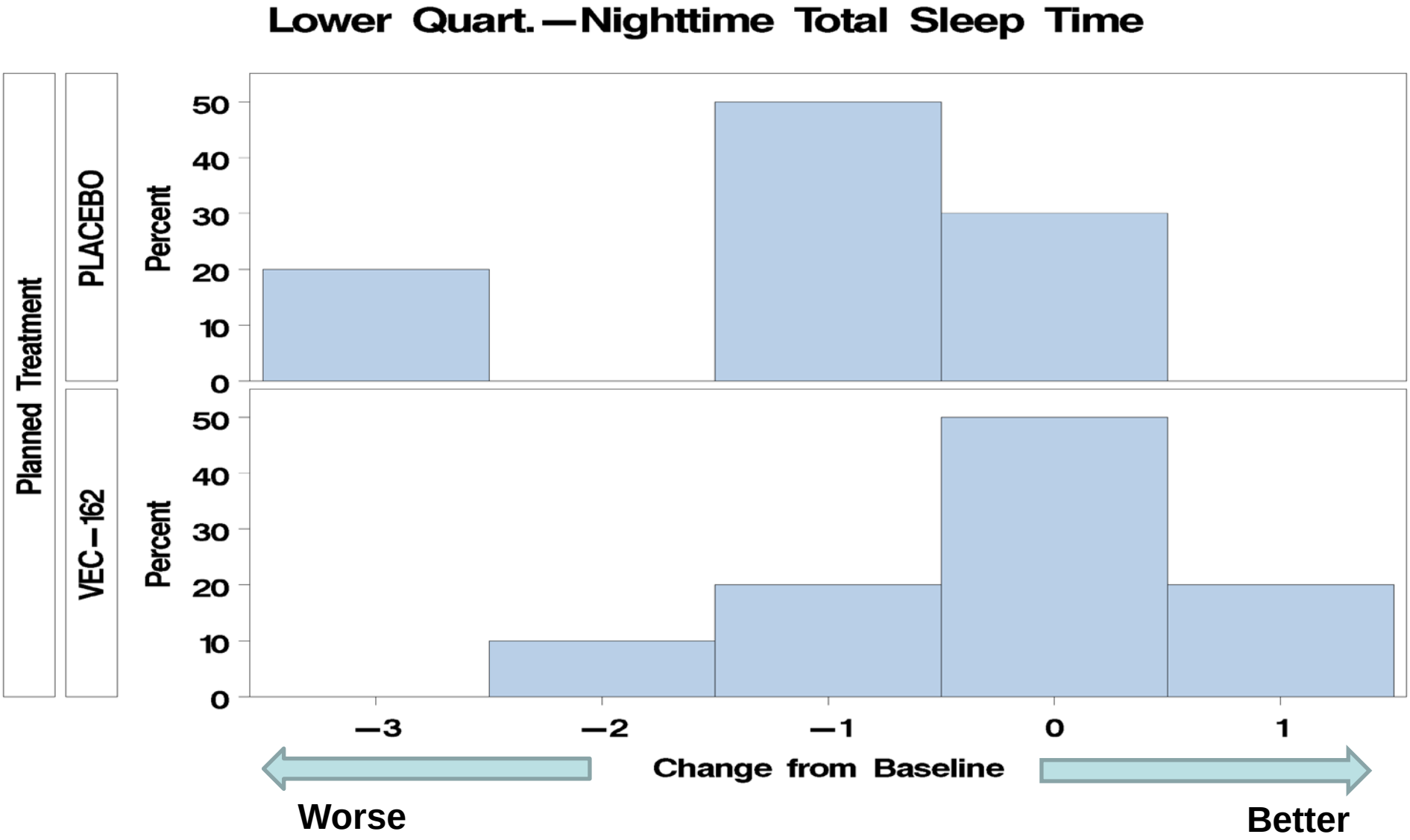
- **ANCOVA analysis on ITT population**

- **Permutation ANCOVA analysis on ITT population**

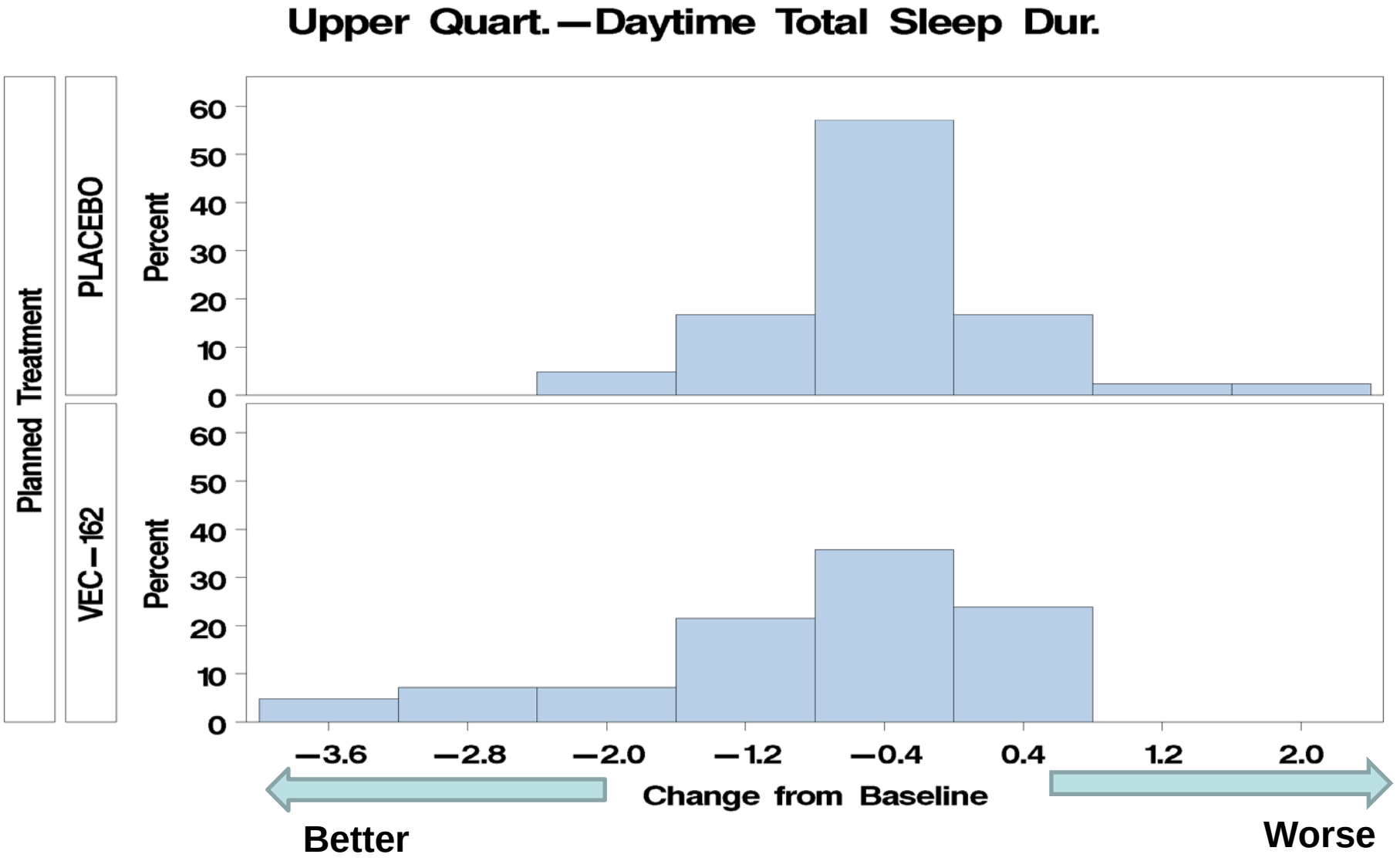
Study 3201 LQ-nTST (Hours)



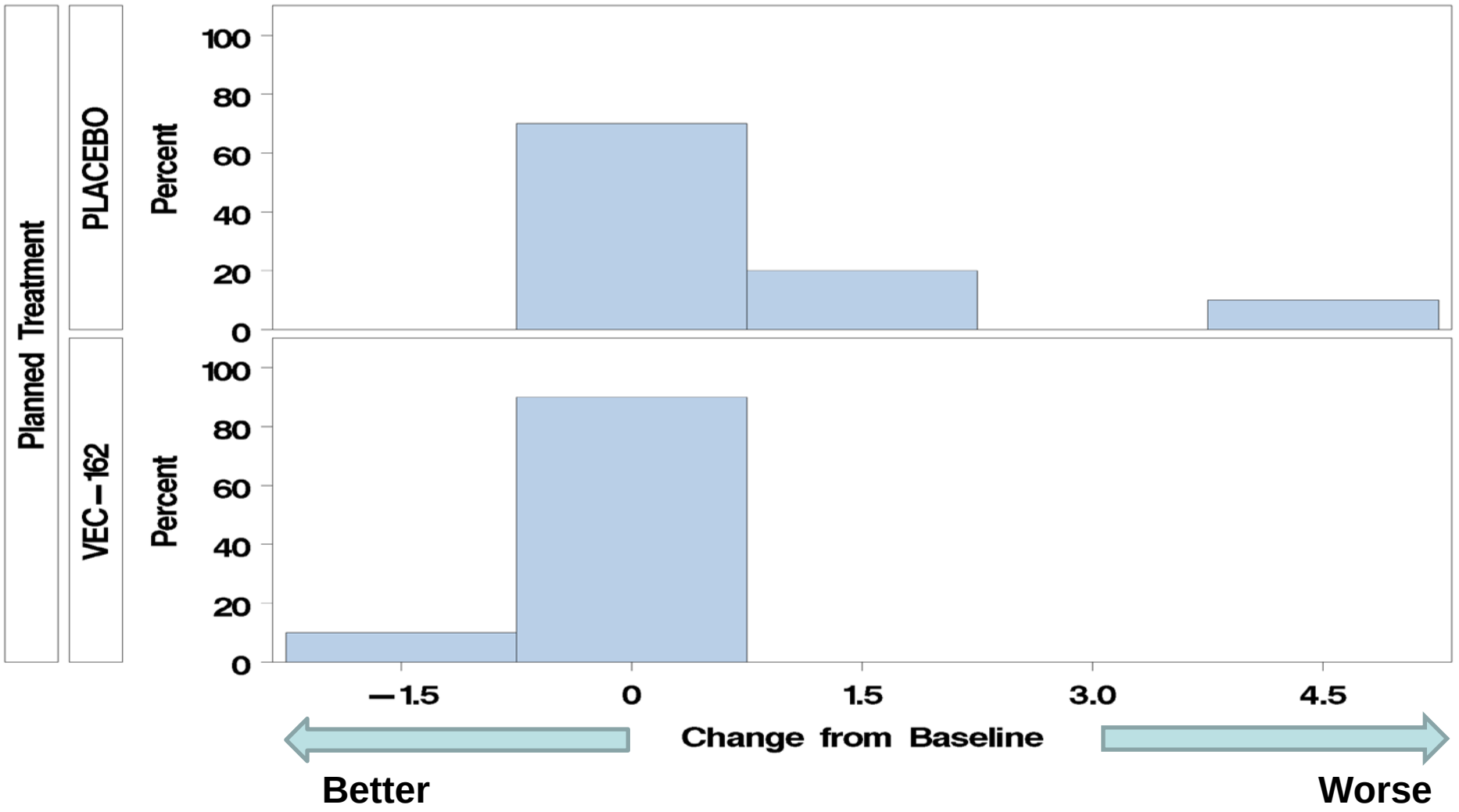
Study 3203 LQ-nTST (Hours)



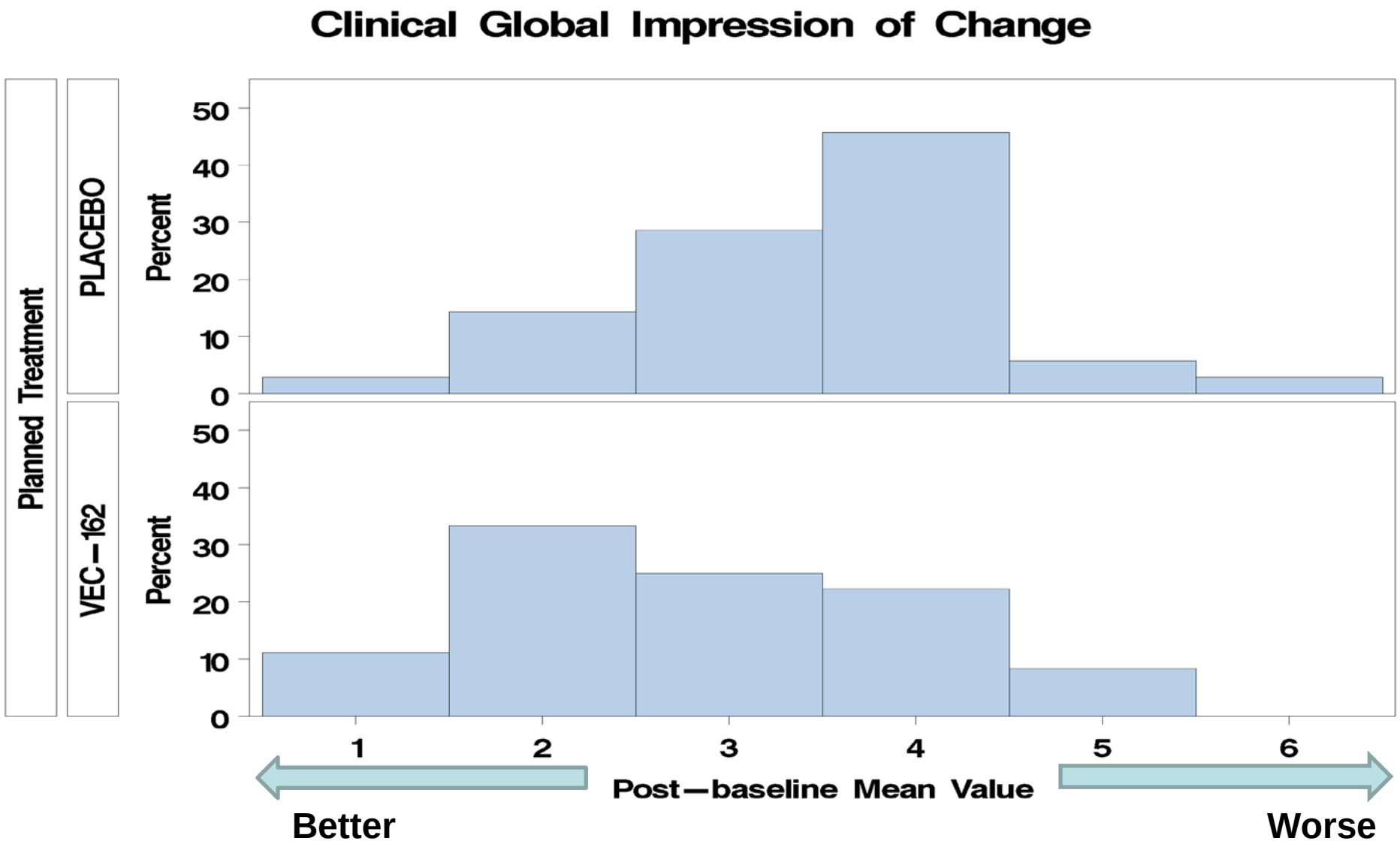
Study 3201 UQ-dTSD (Hours)



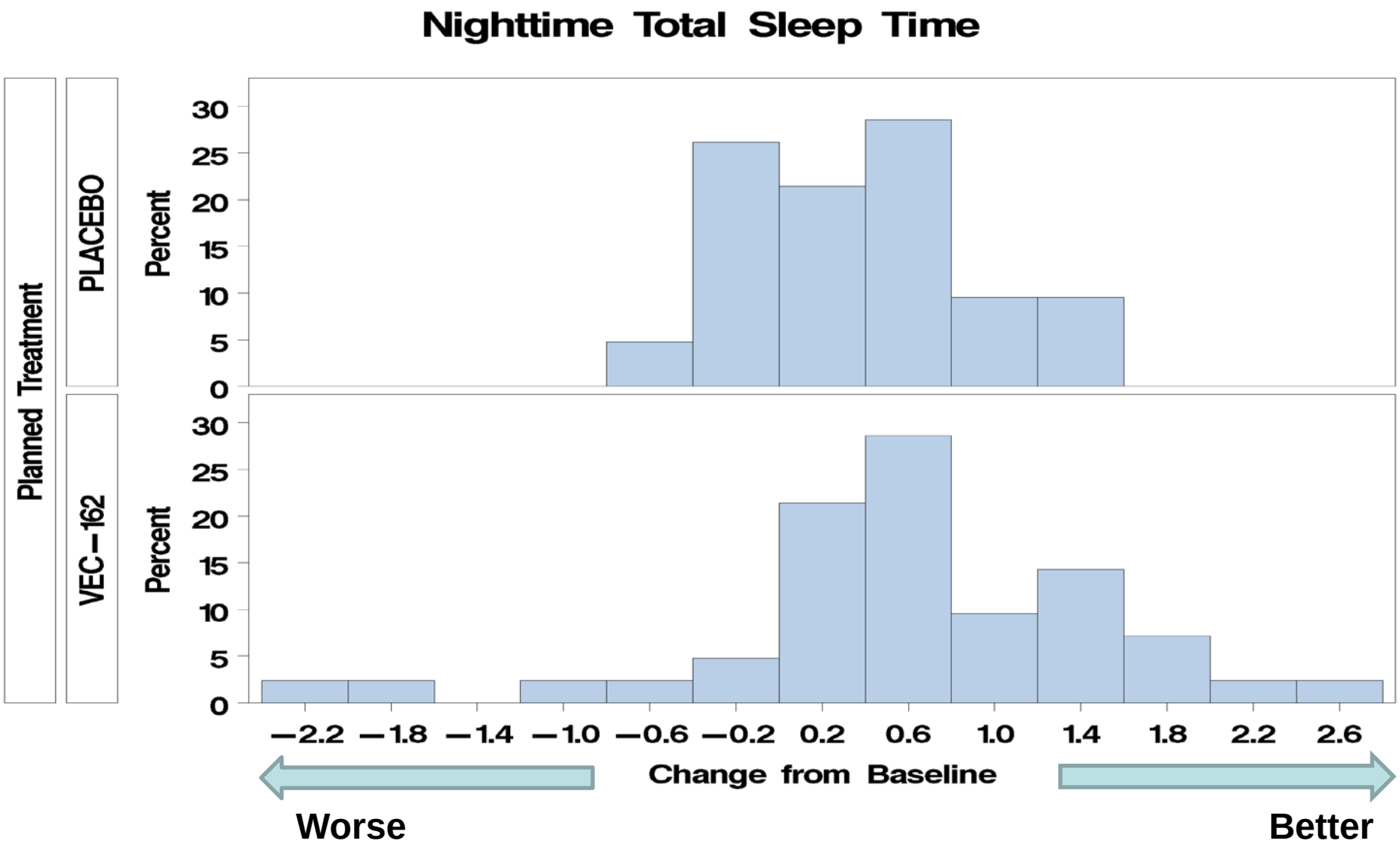
Study 3203 UQ-dTSD (Hours)



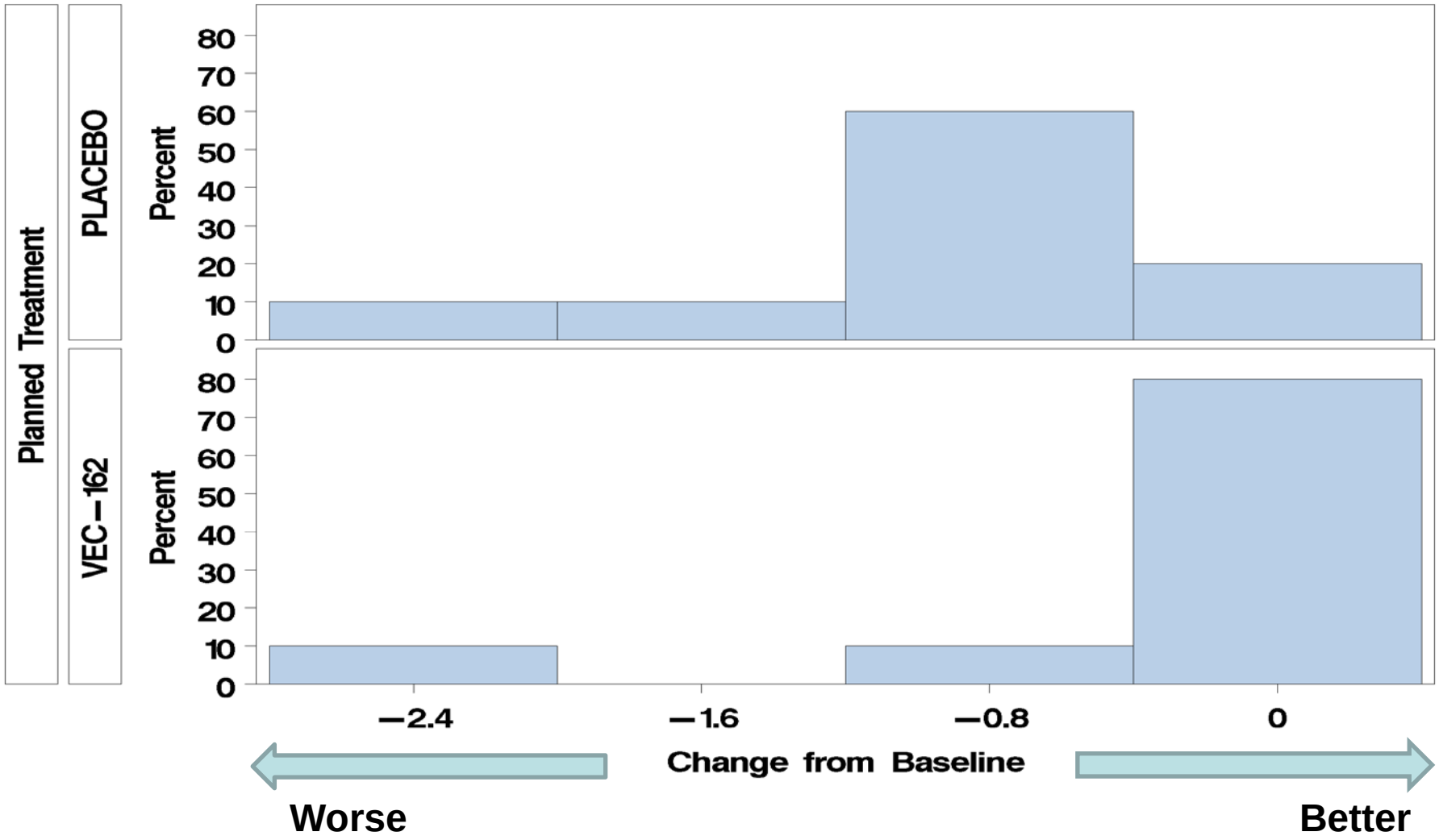
Study 3201 CGI-C



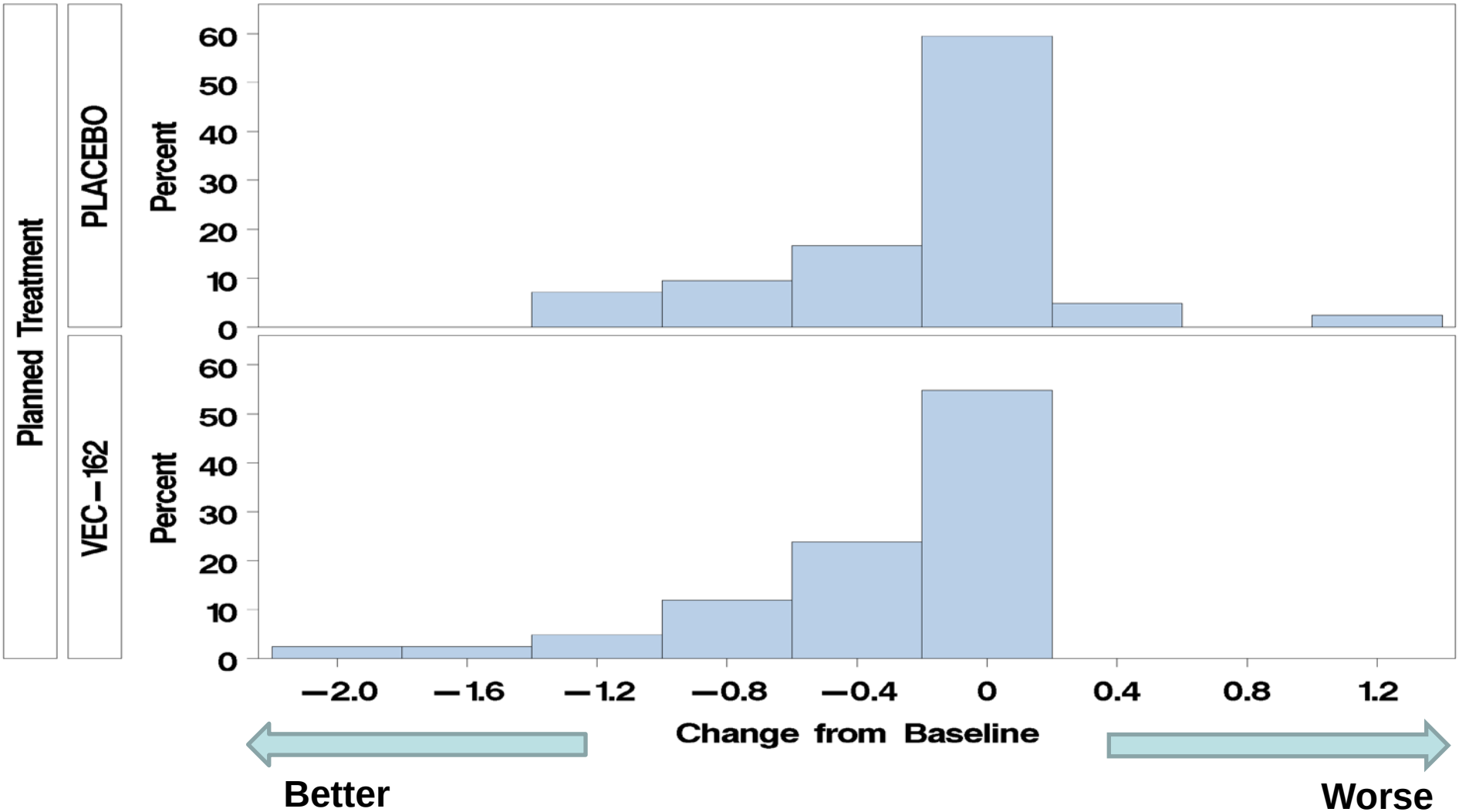
Study 3201 nTST (Hours)



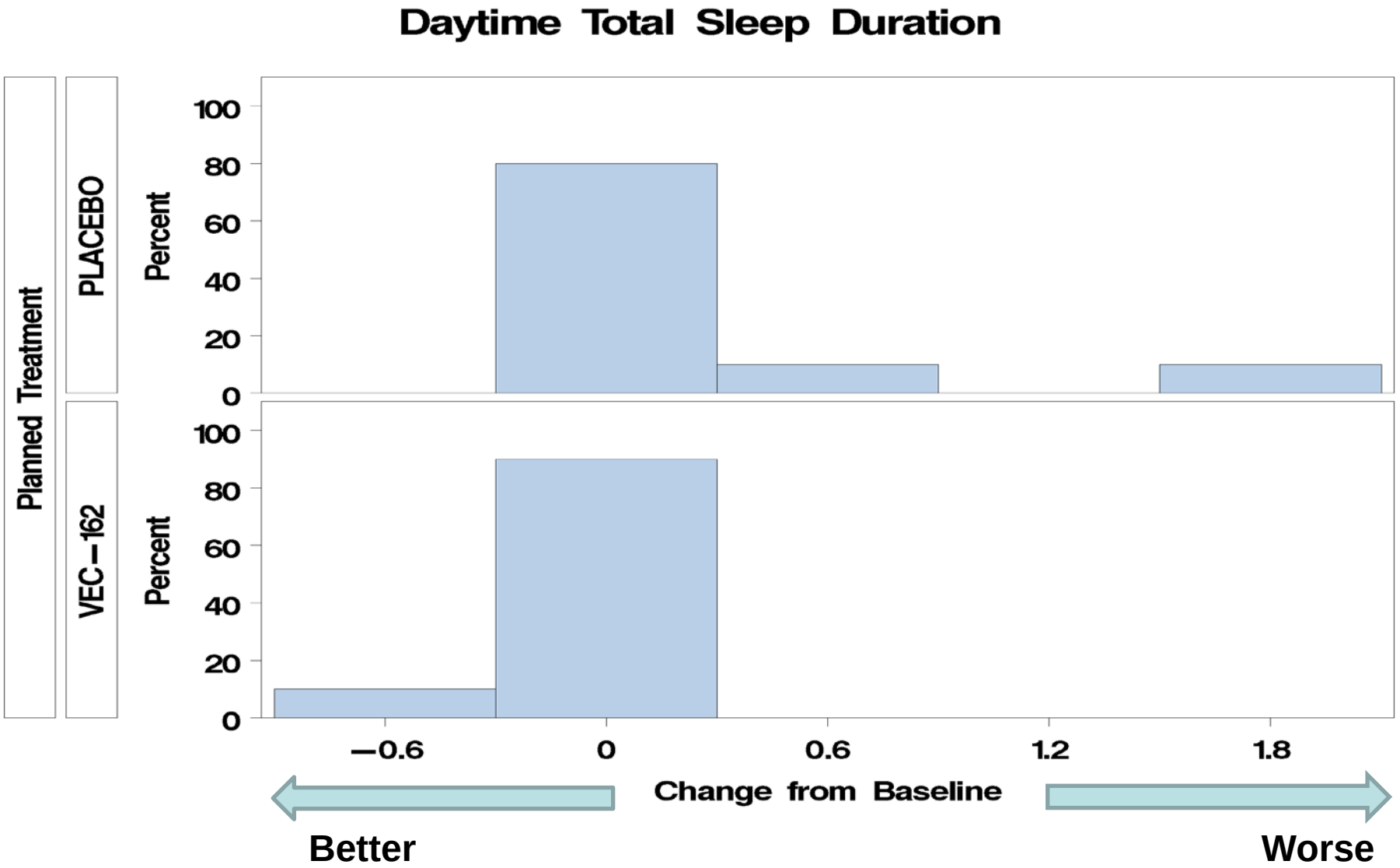
Study 3203 nTST (Hours)



Study 3201 dTSD (Hours)



Study 3203 dTSD (Hours)



12 Patients Excluded by Sponsor (Study 3201)

Subject ID	Treatment Group	Cycle Length	% Cycle Baseline	% Cycle Postbaseline
1	PLACEBO	32	275	53
2	PLACEBO	54	148	13
3	PLACEBO	54	94	11
4	PLACEBO	58	36	129
5	PLACEBO	59	114	27
6	PLACEBO	79	66	161
7	PLACEBO	81	61	146
8	PLACEBO	96	49	79
9	VEC-162	72	71	3
10	VEC-162	85	117	24
11	VEC-162	94	66	107
12	VEC-162	97	85	36

Results of ANCOVA Study 3201, ITT, n=84

Endpoints	LS means Placebo	LS Means Tasimelteon	P-value w/o Site	P-value with Site
LQ-nTST	0.37	0.83	0.051	0.023
UQ-dTSD	-0.36	-0.81	0.012	0.003
CGIC	3.34	2.63	0.008	0.010
nTST	0.35	0.60	0.115	0.066
dTSD	-0.18	-0.36	0.017	0.003

Note: LS means were from the ANCOVA analysis without site.

Results of ANCOVA
Study 3203, ITT, n=20

Endpoints	Placebo	Tasimelteon	P-value
LQ-nTST	-1.23	-0.11	0.023
UQ-dTSD	0.83	-0.16	0.027
nTST	-0.74	-0.20	0.132
dTSD	0.30	-0.05	0.055

Results of Permutation ANCOVA
Study 3201, ITT, n=84

Endpoint	Permutation ANCOVA without Site	Permutation ANCOVA with Site	ANCOVA without Site
LQ-nTST	0.052	0.024	0.051
UQ-dTSD	0.011	0.003	0.012
CGIC	0.008	0.014	0.008
nTST	0.117	0.068	0.115
dTSD	0.015	0.002	0.017

Results of Permutation ANCOVA
Study 3203, ITT, n=20

Endpoint	Permutation ANCOVA	ANCOVA
LQ-nTST	0.023	0.023
UQ-dTSD	0.007	0.027
nTST	0.153	0.132
dTSD	0.022	0.055

Summary

The two studies appear to suggest that tasimelteon 20 mg may be beneficial for Non-24 Hour Disorder in Totally Blind Individuals based on all the clinical endpoints except for nTST (the original primary endpoint).