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GENERIC DRUG NAME: Lorazepam

PROTOCOL NO.: B3541002

PROTOCOL TITLE:

A Multi-Center, Open-Label, Non-Controlled Study to Evaluate the Efficacy and Safety of Lorazepam Intravenously Administered in Subjects With Status Epilepticus or Repetitive Status Epilepticus

Study Centers:

Fifteen (15) centers in Japan took part in this study and enrolled subjects.

Study Initiation and Final Completion Dates:

25 November 2014 and 22 August 2016

Phase of Development:

Phase 3

Study Objective:

The primary objective was to evaluate the efficacy and safety of lorazepam intravenously (IV) administered in subjects with status epilepticus (SE).

METHODS

Study Design:

This was a multi-center, open-label, non-controlled study in Japanese subjects with SE or repetitive SE. The target number of subjects with SE or repetitive SE/cluster seizures who had seizures that could be evaluated by the investigator's visual observations based on motor symptoms was approximately 25 (including at least 3 adult subjects). At least 3 subjects were to be enrolled in the category of nursing infants with the lower age limits 3 months to <1 year. In addition, at least 3 subjects were to be enrolled in the combined categories of infants (1 year to <7 years) and children (7 years to <16 years). At least 5 adult subjects (including at least 3 with motor symptoms) with SE or repetitive SE/cluster seizures who had seizures that could be evaluated by electroencephalogram (EEG) were to be enrolled. The subjects were classified based on age at the initial administration of the study drug (Table 1).

Table 1. Target Number of Subjects With Status Epilepticus or Repetitive Status Epilepticus/Cluster Seizures Who Had the Seizures With Motor Symptoms

Category	Age (At the Initial Administration)	Target Number
Pediatrics		
Nursing infants	3 months to <1 year	At least 3
Infants	1 year to <7 years	At least 3 in total for both categories (infants and children)
Children	7 years to <16 years	
Adults	≥16 years	At least 3
Total	--	25

This study had up to a 6-month screening period, up to a 2-day treatment period and follow-up visit 7 days after the last administration.

The schedule of activities is presented in Table 2.

Table 2. Schedule of Activities

Observation/Assessment	**Screening Period**[a]	**Treatment Period**[b]						**Follow-Up Period**	**Termination**
		Before Initial Dose	**10 Minutes After Dose**	**30 Minutes After Dose**	**2 Hours After Dose**	**12 Hours – 24 Hours After Dose**	**24 Hours – 48 Hours After Dose**	**7 Days After Last Administration**	
Allowable Period	**Up to 6 Months Before Initial Dose**		**10 – 15 Minutes After Dose**	**30 – 40 Minutes After Dose**	**1.75 - 2.25 Hours After Dose**			**±3 Days**	**Within 3 Days**
Informed consent	X	X[a]							
Inclusion/exclusion criteria	X								
Medical history	X								
Weight	(X)	X[c]							
Pregnancy test[d]	(X)	X						X	X
Physical examination (interview)	(X)	X	X	X		X		X	X
Vital signs (blood pressure and pulse rate)[e]	(X)	X	X	X	X	X		X	X
SpO_2[e]		X	X	X	X	X		X	X
Clinical laboratory tests	(X)	X					X		X[f]
Assessment on epileptic seizure		X							
Adverse events		X						X	X
Concomitant drugs and therapy	(X)	X						X	X

Table 2. Schedule of Activities

Abbreviation: SpO_2=arterial oxygen saturation measured by transcutaneous pulse oximetry.

a. In case informed consent was not obtained from the subject during the screening period, the emergency informed consent form was used and informed consent was obtained from a legally acceptable representative/parent(s)/legal guardian before the initial dose. In this case, observations/assessments that were indicated on (X) were only performed before the initial dose of the study drug.
b. The day for the initial dose of the investigational treatment was on Day 1. If a second dose was to be given, the evaluation based on the initial dose were performed before the second dose, and observation/test items "10 minutes after dose" and those after that in the above schedule were performed after the second dose.
c. In the case that the weight could not be measured, the most accurate estimate of the subject's current weight was used.
d. A pregnancy test was performed only in female subjects of childbearing potential.
e. As for vital signs and SpO_2, those continuously monitored by biological information monitors, etc could be used.
f. Only in the case that termination was before the clinical laboratory tests on "24 hours to 48 hours after dose".

Number of Subjects (Planned and Analyzed):

This study planned to enroll approximately 25 subjects with SE or repetitive SE/cluster seizures who had evaluable motor symptoms by investigator's visual observation. A total of 26 subjects were enrolled in the study and treated. All subjects completed the study. A total of 25 subjects were analyzed for efficacy. A total of 26 subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects (either gender) ≥3 months of age with SE or repetitive SE/cluster seizures who had seizures that could have been evaluated by investigator's visual observations based on motor symptoms or who had seizures that could be evaluated by EEG were enrolled in this study.

Main Exclusion Criteria: Subjects with known or suspected recurrent seizures due to illegal drug or alcohol withdrawal, hypersensitivity to lorazepam or benzodiazepine, or benzodiazepine abuse were excluded from the study.

Study Treatment:

For adult subjects (≥16 years), lorazepam 4 mg was IV administered at a slow injection rate of approximately 2 mg/minute. While for pediatric subjects (3 months to <16 years), lorazepam 0.05 mg/kg (but not exceeding 4 mg) was IV administered at a slow injection rate of approximately 2 mg/minute.

For subjects whose seizure did not stop or stopped but recurred within 10 minutes after the initial dose, the second dose could be administered at the same dose and injection rate as the initial dose, at least 10 minutes after the initial dose. For subjects whose seizure stopped but recurred >10 minutes after the initial dose (but within 12 hours of the initial dose), an additional dose could be administered at the same dose and injection rate as the initial dose. A total of 2 doses were permitted in this study.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Proportion of subjects whose seizures stopped within 10 minutes after initial dose and who continued seizure-free for at least 30 minutes after the completion of initial dose (efficacy rate).

Key Secondary Efficacy Endpoint:

- Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 30 minutes.

Other Secondary Efficacy Endpoints:

- (1-1) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (only the initial dose) and who continued seizure-free for at least 12 hours postdose;
- (1-2) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 12 hours post-dose;
- (2-1) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (only the initial dose) and who continued seizure-free for at least 24 hours postdose;
- (2-2) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 24 hours postdose;
- (3-1) Time to resolution of seizures from the administration of study drug (only the initial dose);
- (3-2) Time to resolution of seizures from the administration of study drug (either initial or second dose);
- (4-1) Time to relapse from the resolution of seizures following the administration of study drug (only the initial dose, within 24 hours);
- (4-2) Time to relapse from the resolution of seizures following the administration of study drug (either initial or second dose, within 24 hours).

Safety Evaluations:

Safety evaluations included clinical monitoring, physical examination, vital signs (heart rate, blood pressure), oxygen saturation, adverse events and safety laboratory tests. Safety assessments were performed as shown in Table 2.

Statistical Methods:

Efficacy: The primary analysis population was the full analysis set defined as all subjects who received at least 1 dose of study drug, and excluded subjects whose SE or repetitive SE/cluster seizures was determined by the EEG. The 95% confidence intervals (CIs) were calculated based on the exact CI by the Clopper-Pearson method. For the efficacy rate in the endpoint, the point estimate and 95% CI were presented. For the endpoints of the time resolution of seizures or relapse, the time was descriptively summarized and Kaplan Meier estimates of the time to resolution of seizure or relapse was provided. The efficacy endpoints were presented in subgroups of adult or pediatric subjects; however, 95% CIs were not to be calculated in these subgroups. For the subjects with SE or repetitive SE/cluster seizures who had seizures which were evaluated by EEG, the data were listed by subject.

Safety: The safety data were summarized based on the safety analysis set (SAS) which consisted of all subjects who received at least 1 dose of study drug. The subjects who were enrolled as subjects with SE or repetitive SE/cluster seizures who had seizures which were evaluated by EEG were included in SAS. The safety was analyzed according to the algorithm and formats that were specified according to the sponsor data standards. The last measurement before first dose was defined as baseline. The safety endpoints were presented in subgroups of adult or pediatric subjects.

RESULTS

Subject Disposition and Demography:

Subject disposition is presented in Table 3. A total of 26 subjects were enrolled in the study and treated. All subjects completed the study. One (1) subject was excluded from the efficacy analysis due to SE seizures that were evaluated by EEG. All subjects were analyzed for safety.

Table 3. Subject Disposition

	Lorazepam
Number of subjects assigned to study treatment	26
Treated	26
Completed	26
Discontinued	0
Analyzed for efficacy	
Full analysis set	25
Analyzed for safety	
Adverse events	26
Laboratory data	26
Safety analysis set	26

Overall demographic characteristics are summarized in Table 4. Of the 26 subjects, 10 (38.5%) subjects were adults with mean age 27.6 years while 16 (61.5%) subjects were from the pediatric population with a mean age of 5.4 years.

Table 4. Demographic Characteristics

Number (%) of Subjects	Total	Adults	Pediatrics			
			All	Nursing Infants	Infants	Children
Number of subjects	26	10	16	1	8	7
Sex						
Male	16	6	10	1	4	5
Female	10	4	6	0	4	2
Age						
Mean (SD)	14.0 (12.9)	27.6 (9.9)	5.4 (4.3)	0	2.5 (1.6)	9.6 (2.7)
Median	9.5	27.0	4.5	0	2.0	8.0
Range (min-max)	0-49	17-49	0-13	0-0	1-5	7-13
Race						
Asian	26 (100.0)	10 (100.0)	16 (100.0)	1 (100.0)	8 (100.0)	7 (100.0)
Ethnicity						
Not Hispanic/Latino	26 (100.0)	10 (100.0)	16 (100.0)	1 (100.0)	8 (100.0)	7 (100.0)

Adult: ≥16 years, pediatric: <16 years, nursing infants: 3 months to <1 year, infants: 1 year to <7 years, children: 7 years to <16 years.
Abbreviations: max=maximum; min=minimum; SD=standard deviation.

Efficacy Results:

Primary Endpoint:

Proportion of Subjects Whose Initial Seizure Stopped Within 10 Minutes and who Continued Seizure-Free for At least 30 Minutes After the Completion of Initial Dose:

A total of 12 subjects (48.0%) had initial seizure that stopped within 10 minutes and continued seizure-free for at least 30 minutes after the completion of initial dose (Table 5). The lower bound of 95% CI of the primary efficacy endpoint was lower than 30% (pre-specified expected minimum responder rate).

Table 5. Proportion of Subjects Whose Initial Seizure Stopped Within 10 Minutes and who Continued Seizure-Free for At least 30 Minutes After the Completion of Initial Dose

Total (N=25)		Adults (N=9)	Pediatric (N=16)			
			All (N=16)	Nursing Infants (N=1)	Infants (N=8)	Children (N=7)
N (%)	95% CI	n (%)	n (%)	n (%)	n (%)	n (%)
12 (48.0)	27.8-68.7	6 (66.7)	6 (37.5)	0	4 (50.0)	2 (28.6)

Adult: ≥16 years, pediatric: <16 years, nursing infants: 3 months to <1 year, infants: 1 year to <7 years, children: 7 years to <16 years.
Abbreviations: CI=confidence interval; N/n=number of subjects with observations.

Secondary Endpoints:

Proportion of Subjects Whose Initial Seizure Stopped Within 10 Minutes and who Continued Seizure-Free for a Given Time Period:

A total of 16 subjects (64.0%) had initial seizure stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 minutes to 30 minutes from the initial dose]) and continued seizure-free for at least 30 minutes (Table 6).

Table 6. Proportion of Subjects Whose Initial Seizure Stopped Within 10 Minutes and who Continued Seizure-Free for a Given Time Period

	Total (N=25)		Adults (N=9)	Pediatric (N=16)			
				All (N=16)	Nursing Infants (N=1)	Infants (N=8)	Children (N=7)
	n (%)	95% CI	n (%)	n (%)	n (%)	n (%)	n (%)
Key secondary	16 (64.0)	42.5-82.0	7 (77.8)	9 (56.3)	0	5 (62.5)	4 (57.1)
Secondary 1-1	8 (32.0)	14.9-53.5	4 (44.4)	4 (25.0)	0	3 (37.5)	1 (14.3)
Secondary 1-2	11 (44.0)	24.4-65.1	5 (55.6)	6 (37.5)	0	3 (37.5)	3 (42.9)
Secondary 2-1	6 (24.0)	9.4-45.1	4 (44.4)	2 (12.5)	0	1 (12.5)	1 (14.3)
Secondary 2-2	8 (32.0)	14.9-53.5	4 (44.4)	4 (25.0)	0	1 (12.5)	3 (42.9)

Adult: ≥16 years, pediatric: <16 years, nursing infants: 3 months to <1 year, infants: 1 year to <7 years, children: 7 years to <16 years.
Key secondary: Subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 30 minutes.
Secondary 1-1: Subjects whose seizures stopped within 10 minutes after the administration of study drug (only the initial dose) and who continued seizure-free for at least 12 hours postdose.
Secondary 1-2: Subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 12 hours postdose.
Secondary 2-1: Subjects whose seizures stopped within 10 minutes after the administration of study drug (only the initial dose) and who continued seizure-free for at least 24 hours postdose.
Secondary 2-2: Subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 24 hours postdose.
Abbreviations: CI=confidence interval; N=number of subjects.

Time to Resolution of Seizures From the Administration of Study Drug:

Time to resolution of seizures from the administration of study drug is presented in Table 7.

Median time for the resolution of the seizures was 1 minute for the overall population in subjects with initial dose as well as subjects with either dose (initial or second dose).

Table 7. Time to Resolution of Seizures From the Administration of Study Drug

		Total (N=25)	Adults (N=9)	Pediatric (N=16)			
				All (N=16)	Nursing Infants (N=1)	Infants (N=8)	Children (N=7)
Secondary 3-1	n (%)						
*1		15 (60.0)	6 (66.7)	9 (56.3)	1 (100)	4 (50.0)	4 (57.1)
*2		0	0	0	0	0	0
*3		10 (40.0)	3 (33.3)	7 (43.8)	0	4 (50.0)	3 (42.9)
Time to resolution (minutes)							
Summary statistics	n	15	6	9	1	4	4
	Mean (SD)	2.7 (3.27)	3.2 (3.37)	2.3 (3.35)	2.0 (-)	0.3 (0.50)	4.5 (4.20)
	Median	1	2	1	2	0	4
	Minimum	0	0	0	2	0	0
	Maximum	10	9	10	2	1	10
Kaplan-Meier estimates (percentiles)							
	10%	0	0	0	2	0	0
	25%	1	1	0.5	2	0	3
	50%	5	5	7.5	2	-	10
	75%	-	-	-	2	-	-
	90%	-	-	-	2	-	-
Secondary 3-2	n (%)						
#1		17 (68.0)	7 (77.8)	10 (62.5)	0	5 (62.5)	5 (71.4)
#2		1 (4.0)	1 (11.1)	0	0	0	0
#3		7 (28.0)	1 (11.1)	6 (37.5)	1 (100)	3 (37.5)	2 (28.6)
#4		0	0	0	0	0	0
Time to resolution (minutes)							
Summary statistics	n	17	7	10	0	5	5
	Mean (SD)	2.4 (3.18)	2.7 (3.30)	2.2 (3.26)	-	0.2 (0.45)	4.2 (3.70)
	Median	1	1	0.5	-	0	3
	Minimum	0	0	0	-	0	0
	Maximum	10	9	10	-	1	10
Kaplan-Meier estimates (percentiles)							
	10%	0	0	0	-	0	0
	25%	0	1	0	-	0	3
	50%	3	3	4	-	0.5	5
	75%	-	9	-	-	-	-
	90%	-	-	-	-	-	-

Adult: ≥16 years, pediatric: <16 years, nursing infants: 3 months to <1 year, infants: 1 year to <7 years, children: 7 years to <16 years.

Secondary 3-1: Only the initial dose.

*1 Subjects whose seizure stopped within 10 minutes after the initial dose without receiving the prohibited medications.

*2 Subjects who received the prohibited medications within 10 minutes after the initial dose.

*3 Subjects whose seizure did not stop within 10 minutes after the initial dose.

Secondary 3-2: Either initial or second dose.

#1 Subjects whose seizure stopped within 10 minutes after either initial or second dose without receiving the prohibited medications and took second dose for seizures which were evaluated on EEG.

#2 Subjects who received the prohibited medications within 10 minutes after either initial or second dose.

#3 Subjects whose seizure did not stop within 10 minutes after either initial or second dose.

#4 Subjects who took second dose for seizures which were evaluated on EEG.

Abbreviations: EEG=electroencephalogram; N=number of subjects; n=number of subjects with observations; SD=standard deviation.

Time to Relapse From the Resolution of Seizures Following the Administration of Study Drug:

Time to relapse from resolution of seizures from the administration of study drug is presented in Table 8.

Median time for the relapse of the seizures was 62 minutes for the overall population in subjects with initial dose while 103 minutes for subjects with either initial or second dose.

Table 8. Time to Relapse From the Resolution of Seizures Following the Administration of Study Drug (Within 24 Hours)

		Total (N=25)	Adults (N=9)	Pediatric (N=16)			
				Pediatric (N=16)	Nursing Infants (N=1)	Infants (N=8)	Children (N=7)
Secondary 4-1	n (%)						
*1		6 (24.0)	4 (44.4)	2 (12.5)	0	1 (12.5)	1 (14.3)
*2		9 (36.0)	2 (22.2)	7 (43.8)	1 (100)	3 (37.5)	3 (42.9)
Time to relapse (minutes)							
Summary statistics	n	9	2	7	1	3	3
	Mean (SD)	216.3 (340.07)	83.0 (28.28)	254.4 (382.68)	11 (-)	557.0 (445.17)	33.0 (25.51)
	Median	62	83	49	11	743	23
	Minimum	11	63	11	11	49	14
	Maximum	879	103	879	11	879	62
Kaplan-Meier estimates (percentile)							
	10%	14	63	11	11	49	14
	25%	49	103	23	11	396	18.5
	50%	743	-	62	11	811	42.5
	75%	-	-	879	11	-	-
	90%	-	-	-	11	-	-
Secondary 4-2	n (%)						
#1		8 (32.0)	4 (44.4)	4 (25.0)	0	1 (12.5)	3 (42.9)
#2		9 (36.0)	3 (33.3)	6 (37.5)	0	4 (50.0)	2 (28.6)
Time to relapse (minutes)							
Summary statistics	n	9	3	6	0	4	2
	Mean (SD)	385.0 (454.52)	470.7 (671.76)	342.2 (378.74)	-	492.0 (386.02)	42.5 (27.58)
	Median	103	103	179.5	-	520.0	42.5
	Minimum	23	63	23	-	49	23
	Maximum	1246	1246	879	-	879	62
Kaplan-Meier estimates (percentile)							
	10%	49	63	36	-	49	23
	25%	103	103	62	-	297	62
	50%	1246	-	811	-	743	-
	75%	-	-	-	-	879	-
	90%	-	-	-	-	-	-

Adult: ≥16 years, pediatric: <16 years, nursing infants: 3 months to <1 year, infants: 1 year to <7 years, children: 7 years to <16 years.
Secondary 4-1: Only the initial dose.
*1 Subjects who continued seizure-free for at least 24 hours postdose after the initial dose.
*2 Subjects who did not continue seizure-free for at least 24 hours postdose after the initial dose.
Secondary 4-2: Either initial or second dose.
#1 Subjects who continued seizure-free for at least 24 hours postdose after either initial or second dose.
#2 Subjects who did not continue seizure-free for at least 24 hours postdose after either initial or second dose.
Abbreviations: N=number of subjects; n=number of subjects with observations; SD=standard deviation.

Safety Results:

All-causalities and treatment-related treatment-emergent adverse events (TEAEs) are presented in Table 9. A total of 12 subjects (46.2%) experienced 17 TEAEs of which 4 TEAEs were reported as treatment-related.

The majority of TEAEs were mild or moderate in severity. One (1) TEAE of pneumonia aspiration was considered severe.

No treatment-emergent death was reported in this study. One (1) treatment-emergent serious adverse event of pneumonia aspiration was reported, but it was considered not to be related to treatment. No permanent or temporary discontinuations were reported in the study.

The incidence of all-causalities and treatment-related TEAEs (system organ class and preferred terms) are summarized in Table 9. The most common TEAEs by preferred term were somnolence (2 TEAEs) and insomnia (2 TEAEs).

Table 9. Treatment-Emergent Non-Serious Adverse Events Incidences: All-Causalities and Treatment-Related

Number of Subjects, n (%) System Organ Class Preferred Term	Lorazepam		
	n (%)	n1	n2
Subjects evaluable for non-SAE	26		
Subjects with non-SAE	12 (46.15)		
Gastrointestinal disorders	1 (3.85)	1	0
Vomiting	1 (3.85)	1	0
General disorders and administration site conditions	1 (3.85)	1	0
Pyrexia	1 (3.85)	1	0
Infections and infestations	2 (7.69)	2	0
Pneumonia	1 (3.85)	1	0
Urinary tract infection	1 (3.85)	1	0
Injury, poisoning and procedural complications	1 (3.85)	2	0
Fall	1 (3.85)	1	0
Laceration	1 (3.85)	1	0
Investigations	1 (3.85)	1	0
Blood creatine phosphokinase increased	1 (3.85)	1	0
Nervous system disorders	4 (15.38)	4	4
Ataxia	1 (3.85)	1	1
Balance disorder	1 (3.85)	1	1
Somnolence	2 (7.69)	2	2
Psychiatric disorders	2 (7.69)	2	0
Insomnia	2 (7.69)	2	0
Renal and urinary disorders	1 (3.85)	1	0
Pollakiuria	1 (3.85)	1	0
Respiratory, thoracic and mediastinal disorders	1 (3.85)	1	0
Epistaxis	1 (3.85)	1	0
Skin and subcutaneous tissue disorders	1 (3.85)	1	0
Erythema	1 (3.85)	1	0

Except for 'n1' and 'n2', subjects were only counted once per treatment for each row.
Included data up to 999 days after last dose of study drug.
Occurrences were calculated as the number of records having distinct value of subject ID, start of AE, severity, causality and treatment group for that preferred term.
MedDRA (V19.1) coding dictionary applied.
Abbreviations: AE=adverse event; ID=identification; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities; n1=number of occurrences of treatment-emergent all-causalities adverse events; n2=number of occurrences of treatment-emergent causally related to treatment adverse events; SAE=serious adverse event; V=version.

No clinically significant changes were observed in the laboratory parameters or vital signs data during study.

CONCLUSIONS:

- Proportion of subjects whose initial seizure stopped within 10 minutes and who continued seizure-free for at least 30 minutes after the completion of initial dose was 48.0% (12/25, 95% CI: 27.8%-68.7%). The lower bound of 95% CI of the primary efficacy endpoint was lower than 30% (pre-specified expected minimum efficacy rate).

- Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 30 minutes was 64.0% (16/25, 95% CI: 42.5%-82.0%).

- The most common TEAEs were somnolence (7.7%, 2/26) and insomnia (7.7%, 2/26), and the most common treatment-related TEAE was somnolence (7.7%, 2/26). Almost all TEAEs were mild or moderate in severity.

- No subject experienced serious or severe treatment-related TEAEs nor discontinued the study due to TEAEs.

- Lorazepam was safe and well tolerated in the adult and pediatric populations.