CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 209566 / Serial Number 0001 -
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Applicant:	Meridian Medical Technologies
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1 EXECUTIVE SUMMARY

This NDA submission is to seek 505(b)(2) pathway approval of Midazolam Multi-use Vials for Intramuscular Manual (IM) Injection to be used in ambulance settings by paramedics to treat patients with Status Epilepticus(SE) during their transportation to hospitals.

SE (Status Epilepticus) is when a seizure lasts longer than 5 minutes or when seizures occur close together and the person doesn't recover between seizures. It is a medical emergency associated with significant morbidity and mortality. The study doses were assigned based on subject body weight estimates.

The efficacy evidence was from one legacy study RAMPART (the Rapid Anticonvulsant Medication Prior to ARrival Trial).

1.1 Conclusions and Recommendations

The pivotal study in patients with SE presented statistical evidence that Midazolam, at body weight based dosing of 10 mg, or 5 mg, administered by IM auto-injector by paramedics in an ambulance setting is efficacious for the treatment of SE based on increased rate of seizure cessation upon arrival at the hospital ED (Emergency Department). The IM Midazolam showed an efficacy result better than that of the active control drug IV Lorazepam, while the active control drug showed an efficacy result close to the previously observed response rate for this currently approved drug for SE. (Please see reference [1].)

1.2 Brief Overview of Clinical Study RAMPART

The Phase 3 study RAMPART was a multi-center, randomized, double-blinded, parallel group and active controlled study to evaluate the efficacy of IM midazolam versus IV lorazepam in the prehospital treatment of status epilepticus by paramedics.

This study was designed and conducted by the Neurological Emergencies Treatment Trials (NETT) network, a multi-disciplinary clinical trials infrastructure funded by the National Institute of Neurological Disorders and Stroke (NINDS). Auto-injectors with active medication and placebo were purchased by the Department of Defense and provided to the NINDS through a cooperative agreement.

This study is complete and the study report is included in the current submission.

1.3 Statistical Issues and Findings

No major statistical issues were found.

2 INTRODUCTION

There were two related IND numbers: IND 123121 under the current sponsor Meridian and IND 102254 under the sponsorship of University of Michigan.

One legacy study RAMPART was included in this statistical review for efficacy evaluation. This study was originally designed as a research study.

This drug development program has its origin with army research background therefore the documentation associated with the original research IND 102254 were not searchable in the EDR system (likely classified) by the statistical reviewer (including the team leader).

The commercial IND 123121 has 9 submissions numbered from 0 to 8 between 8/11/2015 and 10/13/2016. The study itself was conducted between 6/15/2009 and 4/10/2011 with the NEJM paper published on 2/16/2012. (Please see reference [2].)

The current NDA 209566 has submissions numbered from 0 to 10 between 11/16/2017 and 8/17/2018. Within the NDA submission, it was claimed that there were pre-specified protocol and SAP which should be dated prior to the study completion, at least prior to early 2012 when the paper based on the study got published. In general, we require the study protocol and statistical analysis plan finalized prior to data un-blinding. But so far I could not verify from our end of record keeping. Please see the clinical review for more details on the regulatory history.

2.1 Overview

Midazolam Multi-use Vials for IM Injection is a practical alternative to the intravenous lorazepam for paramedics to use in the pre-hospital setting for two reasons: it is easier and quicker to administer than a benzodiazepine requiring the intravenous route, and it has longer shelf-life when not-refrigerated. Early termination of prolonged seizures improves overall patient outcomes in SE.

Table 1 List of All Studies included in Review

Study Number	Phase and Design	Treatment Period	Dose Levels	# of Subjects per Arm	Study Population
RAMPART	Phase 3, MC, R, DB, PG, AC trial	Ambulance setting during the transportation of the patient to hospital, usually within the range of minutes to at most one hour	Two dose tiers: 10 mg, or 5 mg based on body weight estimate	448 in treatment group 445 in active control group	Children with estimated body weight of 13 kg or more and adults with SE

MC: multi-center, R: randomized, DB: double-blinded, PG: parallel group, AC: active controlled.

The RAMPART study was multi-center, randomized, double-blinded, parallel group and active controlled. This one phase 3 study was the single pivotal study to support efficacy claim.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form.

At the time of review the following is the link to the EDR Location:
\\CDSESUB1\evsprod\NDA209566\0001

3 STATISTICAL EVALUATION

One study RAMPART is included in this statistical review for efficacy evaluation.

3.1 Data and Analysis Quality

There are some minor issues with the data quality in this study RAMPART.

(1) There were discrepancies in records between seizure termination upon arrival to ED per ED physician (as recorded on the ED arrival form) and the audio recording from the paramedics. However, the protocol has been amended so that the seizure cessation status is based on hospital records instead of the audio recordings.

(2) Subjects were assigned a different ID (Identification) number at each enrollment. The sponsor has created a patient chart listing the repeated ID numbers for the patients from the two sites inspected from which I verified that only the first enrollment was included in the study analysis.

(3) There were discrepancies in the drug disposition records which were documentation errors occurred early in the trial as new study forms were being created.

(4) The audio recording quality was so poor that the statement of seizure termination was not clearly verbalized for many patients.

The primary endpoint of seizure cessation no longer uses information from the audio recording alone but uses the hospital records first than the audio recordings if the hospital records are missing. The key secondary in the study objective to assess the rapidity of the onset of the efficacy, which depends on the audio data, has been removed in this NDA application. The sponsor has submitted a central reader data file which I was able to explore and it seems that it is in line with the site inspection findings that a high percentage of the recordings are not verbally clear due to background noise. Please see appendix tables.

We raised the primary end point data collection as a potential issue at the mid-cycle meeting. We were concerned that the protocol amendment to use hospital records instead of voice recordings might be a post-hoc change. The clinical team has confirmed that this change was acceptable for clinical reasons. Please refer to the clinical review for more details.

In summary, the above data quality issue appears to be minor, and does not seem to affect the primary analysis.

3.2 Evaluation of Efficacy Study – RAMPART

3.2.1 Study Design and Endpoints

The study RAMPART was a phase 3, multicenter, randomized, double-blind, active-control, parallel group study of subjects with status epilepticus. The study was conducted at 17 sites in US alone.

The purpose of this study was to evaluate the efficacy of IM midazolam compared to the active control IV lorazepam in the pre-hospital treatment of status epilepticus.

Eligible patients were those who were having convulsive seizures at the time of treatment by paramedics and were reported by reliable witnesses to have had continuous convulsive seizures for longer than 5 minutes or to have had intermittent seizures for longer than 5 minutes without regaining consciousness.

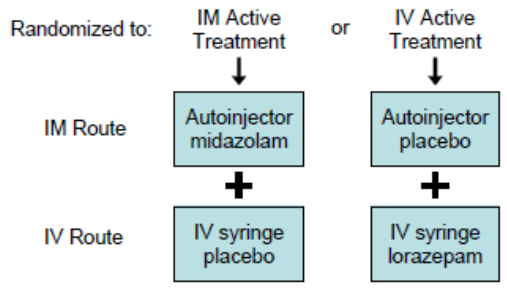
The study population included children with a minimum estimated weight of 13 kg and adults.

Approximately 800 eligible subjects were planned to be randomized with a ratio of 1:1 to the active control IV lorazepam, or the drug IM midazolam.

Due to the nature of the disease and potential ethical issues, the study design has the following four special aspects:

1) There was **no placebo** group, but only an active control group in the study design because it is unethical to give patients placebo when they are having status epilepticus.
2) The patient **consent** process happened as follow-up after the treatment which received exception due to the unconscious state of the patient at the time of enrollment and the emergent nature of the disease since delays in treatment of just a few minutes may increase morbidity and mortality.
3) For the **randomization**, the study utilized a **double-dummy double-blind** design.

Figure 1 Double-Dummy Double-Blind Design – Study RAMPART



(Source: study protocol.)

The study drug and the active control drug were pre-prepared as a study drug kit contained in an instrumented study box at a centralized pharmacy and equipped to the ambulance vehicles randomly. The study boxes were assembled with equal numbers containing study drug and active control drug. Subjects were allocated in an approximately 1:1 randomization to either treatment group as result of the study box carried by the EMS crew, who were blinded to the identity of the study medication.

4) The patient **eligibility** determination and **data collection** methods were also designed to accommodate the emergent nature of this disease indication. The initial assessment of the subject when paramedics arrived at the scene was to follow their EMS protocols. When the EMS crew determined that the subject was **eligible** for the study, the study box was opened. This initiated a timer as well as a **voice recorder**. Paramedics were instructed to verbally indicate when each treatment was administrated, when any rescue treatments were given, and when seizures were terminated. Each statement was time-stamped by the study box relative to time zero of study box opening,

The **primary endpoint** for this study was the binary outcome variable measuring whether there was termination of convulsive seizure activity prior to arrival to the emergency department after an initial dose of study drug without the need of rescue medication.

The planned **key secondary** endpoints on rapidity of the drug effect were **removed** due to data quality issues. Instead, two secondary endpoints (the hospitalization and ICU admission rate) were presented as key secondary endpoints in this NDA application.

However, these two endpoints were not part of a plan to control for overall Type I error. There was one secondary endpoint listed before these two on the list of objectives that did not show any difference between the two treatment groups. Even though we understand that this was planned as a research study and there was no requirement for such control for multiple comparisons, we still think it necessary to adjust for multiplicity in a pivotal study for market approval.

It seems that the voice recording process may need some technical improvements either at the time of recording or the time of deciphering in order to improve the rate of clear verbal statements. The consent process may also need some improvement by using more wristlet medical tags if possible since the patient is very likely to be unconscious at the time of enrollment and treatment. Both could be recommended for consideration if similar trails would be proposed by a commercial sponsor in the future.

3.2.2 Statistical Methodologies

The primary endpoints were analyzed using a Fisher's exact test comparing the drug group versus the active control group. Efficacy analyses were based on the ITT population. Subjects were grouped based on the assigned treatment.

There is **no need for multiplicity adjustment** because only 1 primary endpoint analysis was performed to show statistical significance. There is **no need to consider missing data** for the primary endpoint because the hospital ED (Emergency Department) records were used to determine the seizure cessation status.

The original SAP for the research purpose used a non-inferiority test to compare the two treatment groups, and superiority test as secondary analysis. For this NDA submission, the sponsor has amended the SAP to use superiority test as the primary analysis method to meet the regulatory requirement.

3.2.3 Patient Disposition, Demographics and Baseline Characteristics

This study had its first subject enrolled on 15 June 2009, and the last subject completed on 10 April 2011, for a study period of 95 weeks. The study report was created on the date of 12 December 2012.

There were 893 unique patients: 448 to IM midazolam and 445 to IV lorazepam in the study.

The ITT population consisting of all randomized patients who received the assigned treatment (in this case who had an auto-injector applied regardless of whether the drug was delivered) was used for efficacy data analyses

Table 2 Subject Dispositions - Study RAMPART

Category	IM Midazolam	IV Lorazepam	Total
Enrollments/randomizations	514 (100.0)	509 (100.0)	1023 (100.0)
Re-enrollments	66 (12.8)	64 (12.6)	130 (12.7)
Included in ITT Population	**448 (87.2)**	**445 (87.4)**	**893 (87.3)**
Did not receive IM injection per ED	4 (0.8)	0 (0.0)	4 (0.4)
Did not receive IV injection per ED	253 (49.2)	172 (33.8)	425 (41.5)
Seizure stopped prior to IV start	197 (38.3)	109 (21.4)	306 (29.9)
Medics unable to start IV prior to ED arrival	41 (8.0)	49 (9.6)	90 (8.8)
Other	15 (2.9)	14 (2.8)	29 (2.8)
Reason for end of study			
Discharged from emergency department without hospital admission	209 (40.7)	173 (34.0)	382 (37.3)
Hospital discharge	263 (51.2)	300 (58.9)	563 (55.0)
Hospital admission for 90 days	1 (0.2)	0 (0.0)	1 (0.1)
Death	11 (2.1)	8 (1.6)	19 (1.9)
Consent withdrawn/declined due to an adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn/declined for other reason	12 (2.3)	11 (2.2)	23 (2.2)
Lost to follow up	0 (0.0)	1 (0.2)	1 (0.1)
Other	18 (3.5)	16 (3.1)	34 (3.3)
Total Deaths	11 (2.1)	9 (1.8) *	20 (2.0) *

(Source: modified from the Table 2 in the sponsor's study report.)

Age, gender and race/ethnicity variables appear to be reasonably balanced between the two treatment groups for the ITT population.

Table 3 Subject Demographics - Study RAMPART

	IM Midazolam	IV Lorazepam	Total
N	448	445	893
Age (years)			
Mean (SD)	42.7 (21.55)	44.0 (22.12)	43.4 (21.84)
Age category, n (%)			
0 <= age < 2 years	6 (1.3)	2 (0.4)	8 (0.9)
2 <= age < 6 years	26 (5.8)	27 (6.1)	53 (5.9)
6 <= age < 12 years	16 (3.6)	20 (4.5)	36 (4.0)
12 <= age < 17 years	9 (2.0)	7 (1.6)	16 (1.8)
17 <= age < 65 years	330 (73.7)	317 (71.2)	647 (72.5)
Age >= 65 years	61 (13.6)	72 (16.2)	133 (14.9)
65 <= age < 75 years	30 (6.7)	44 (9.9)	74 (8.3)
Age >= 75 years	31 (6.9)	28 (6.3)	59 (6.6)
Gender, n (%)			
Male	250 (55.8)	238 (53.5)	488 (54.6)
Female	198 (44.2)	207 (46.5)	405 (45.4)
Ethnicity, n (%)			
Hispanic or Latino	49 (10.9)	57 (12.8)	106 (11.9)
Not Hispanic or Not Latino	310 (69.2)	290 (65.2)	600 (67.2)
Unknown/not reported	89 (19.9)	98 (22.0)	187 (20.9)
Race, n (%)			
American Indian/Alaska Native	3 (0.7)	5 (1.1)	8 (0.9)
Asian	8 (1.8)	14 (3.1)	22 (2.5)
Black/African American	229 (51.1)	224 (50.3)	453 (50.7)
Native Hawaiian/Other Pacific Islanders	2 (0.4)	1 (0.2)	3 (0.3)
White	165 (36.8)	183 (41.1)	348 (39.0)
More than one race	9 (2.0)	5 (1.1)	14 (1.6)
Other	7 (1.6)	2 (0.4)	9 (1.0)
Unknown/not reported	25 (5.6)	11 (2.5)	36 (4.0)

(Source: modified from the Table 3 in the sponsor's study report. Reviewer has verified the result.)

Overall, the treatment groups appear to be well balanced with regards to the clinical characteristics of the seizures experienced. In total, 293 (65.4%) subjects in the IM midazolam group and 295 (66.3%) subjects in the IV lorazepam group had a prior history of epilepsy.

Table 4 Summary of Data Related to Seizure – Study RAMPART

	IM Midazolam	IV Lorazepam	Total
	448	445	893
Diagnosis at time of discharge or end of study			
Seizure-related diagnosis including *status epilepticus*	404 (90.2)	399 (89.7)	803 (89.9)
Unable to determine from medical record	13 (2.9)	14 (3.1)	27 (3.0)
Non-epileptic spell	31 (6.9)	32 (7.2)	63 (7.1)
Type of non-epileptic spell			
Pseudo-seizures	27 (6.0)	24 (5.4)	51 (5.7)
Other seizure mimic or non-epileptic coma	4 (0.9)	8 (1.8)	12 (1.3)
Prior history of epilepsy			
No	111 (24.8)	103 (23.1)	214 (24.0)
Yes	293 (65.4)	295 (66.3)	588 (65.8)
Not specified	44 (9.8)	47 (10.6)	91 (10.2)
Precipitant of this episode in subjects with prior epilepsy			
Anticonvulsant withdrawal/ noncompliance	137 (30.6)	141 (31.7)	278 (31.1)
Idiopathic or refractory breakthrough seizures from prior pathology	121 (27.0)	121 (27.2)	242 (27.1)
Acute threshold-lowering co-morbidities	33 (7.4)	29 (6.5)	62 (6.9)
Not applicable/not specified	157 (35.0)	154 (34.6)	311 (34.8)
Acute precipitant of this episode of seizure/*status epilepticus*			
Febrile seizure	14 (3.1)	11 (2.5)	25 (2.8)
Metabolic	21 (4.7)	12 (2.7)	33 (3.7)
Toxic	29 (6.5)	33 (7.4)	62 (6.9)
CNS infection	3 (0.7)	3 (0.7)	6 (0.7)
CNS tumor	10 (2.2)	13 (2.9)	23 (2.6)
Stroke (including ICH/SAH)	20 (4.5)	9 (2.0)	29 (3.2)
Trauma	2 (0.4)	1 (0.2)	3 (0.3)
Acute precipitant of this episode of seizure/*status epilepticus*			
Hypoxic ischemic encephalopathy	1 (0.2)	1 (0.2)	2 (0.2)
Unknown/idiopathic	26 (5.8)	31 (7.0)	57 (6.4)
Other identified acute precipitant	18 (4.0)	18 (4.0)	36 (4.0)
Not applicable/not specified	304 (67.9)	313 (70.3)	617 (69.1)
Emergency department discharge status			
Not admitted to hospital	186 (41.5)	150 (33.7)	336 (37.6)
Admitted directly to ICU	128 (28.6)	161 (36.2)	289 (32.4)
Admitted to another unit of hospital	130 (29.0)	131 (29.4)	261 (29.2)
Not applicable/not specified	4 (0.9)	3 (0.7)	7 (0.8)

(Source: Table 4 from the sponsor's study report.)

3.2.4 Results and Conclusions

The primary outcome was the binary outcome variable measuring whether there was termination of convulsive seizures prior to arrival in the emergency department after an initial dose of study drug without the need for paramedics to administer rescue medication.

Seizures were absent without rescue therapy at emergency department arrival for 329 (73.4%) subjects who were randomized to receive IM midazolam and 282 (63.4%) subjects who were randomized to receive IV lorazepam. The absolute difference in the percentage of subjects who met the primary outcome was 10.1%.

The Fisher's exact test produced a p-value of 0.002.

Table 5 Primary Endpoint Analyses – Study RAMPART

Seizures terminated, no rescue therapy given	**IM Midazolam**	**IV Lorazepam**
No. (%) of subjects achieving treatment success	329 (73.4)	282 (63.4)
95% confidence limits	(69.3, 77.5)	(58.9, 67.8)
P-value for treatment difference (Fisher's exact test)	0.002	

(Source: Table 5 from the sponsor's study report, the reviewer has verified the numbers.)

It is worth noting that the active control group (IV Lorazepam) in this study produced a result of 63.4% seizure cessation rate that is quite close to the previously observed response rate for this currently approved drug for status epilepticus. (Please see reference [1].)

The afore mentioned minor data quality issues appear to affect both treatment groups, and so do the limitations on the study design such as consent after randomization due to the emergent nature of the disease. There is no evidence to suggest that these issues happen to only one of the two treatment groups.

In addition, the Fisher's exact test is the more conservative test and it still produced a small p-value.

The primary result did not change if each of the 17 study sites were removed one at a time by my own independent calculation. So, no single site contributed a significantly larger treatment effect to the overall study result comparing to other sites. The study result can be viewed as consistent across all sites.

Therefore, we consider the study result sufficient evidence to support the efficacy claim.

3.3 Evaluation of Safety

Please refer to the clinical review for details on safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region

In the RAMPART study, the median age of the subjects was about 46 years, with the percentage of female as 44% in the drug group and 47% in the active control group, and the majority being either black or white, with the percentage of being white 37% and 41%, being black as 51% and 50%.

There is no need to subgroup by region, since the entire study was conducted in the US.

Table 6 Age, Gender and Race Summaries by Treatment Group - Study RAMPART

	Age (Median)	Gender (%F)	Race (%White)	Race (%Black)
IM Midazolam	46.0	44.2	36.8	51.1
IV Lorazepam	46.0	46.5	41.1	50.3

(Reviewer's result.)

For the RAMPART study, analyses for the treatment effect of IM Midazalom versus IV Lorazepam on seizure termination rate across clinically meaningful subgroups such as age, gender, and race were performed.

Table 7 Findings in Subgroup Populations – Age, Gender and Race – Study RAMPART

Seizure Termination	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Age < Median			**Age >= Median**					
IM Midazolam	220	167	75.9%	228	162	71.1%			
IV Lorazepam	216	155	71.8%	229	127	55.5%			
	Gender = Female			**Gender = Male**					
IM Midazolam	198	147	74.2%	250	182	72.8%			
IV Lorazepam	207	136	65.7%	238	146	61.3%			
	Race = White			**Race = Black**			**Race = All Other**		
IM Midazolam	165	118	71.5%	229	168	73.4%	54	43	79.6%
IV Lorazepam	183	117	63.9%	224	141	63.0%	38	24	63.2%

(Reviewer's result)

The trend in treatment success appears to be similar across subgroups.

4.2 Other Special/Subgroup Populations

The age range for the subjects in this study covered from a minimum of 0 years old to a maximum of 90 years old.

For regulatory purposes, we usually divide target population into pediatrics, adults and geriatrics. However, this was not included in the design phase for this study. I have performed the subgroup analyses based on these three age categories.

This was to be treated as nominal descriptive result only and not recommended for labeling purpose. The study result in the subgroup of adults seems to be consistent with the overall result. The sample sizes in the subgroup of pediatrics and geriatrics both seem to be too small to draw any inference.

Table 8 Findings in Subgroup – Age Category - Study RAMPART

Seizure Termination	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Pediatrics 0 <= Age < 18			**Adults 18 <= Age < 65**			**Geriatrics Age >= 65**		
IM Midazolam	60	41	68.30%	327	252	77.10%	61	36	59.00%
IV Lorazepam	60	43	71.70%	313	205	65.50%	72	34	47.20%

(Reviewer's result)

By design, the assignment of subjects to dose tier (high or low) was based on body weight estimates. The majority of the subjects received the high dose. The study result in the high dose subgroup seems to be consistent with the overall result. The sample size in the low dose subgroup seems to be relatively small and the result can only be viewed as descriptive.

Table 9 Findings in Subgroup – Dose tier – Study RAMPART

Seizure Termination	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	High Dose			**Low Dose**		
IM Midazolam	386	287	74.4%	62	42	67.7%
IV Lorazepam	386	241	62.4%	59	41	69.5%

(Reviewer's result)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were identified.

5.2 Collective Evidence

Collective evidence is not considered in this review since there was only a single Phase 3 study.

The study provided evidence of efficacy of IM midazolam by paramedics to treat patients with SE (Status Epilepticus) during their transportation to hospitals. The primary analysis p-value is quite small at 0.002.

5.3 Conclusions and Recommendations

The efficacy results obtained from the statistical analyses of the study support the conclusion that IM midazolam is effective in treating patients with Status Epilepticus by paramedics during their transportation to hospitals.

5.4 Labeling Recommendations

Table 10 Efficacy Result from RAMPART Study

	IM midazolam (n=448)	**IV lorazepam (n= 445)**
Outcome Success: Seizures terminated, no rescue therapy given		
No. (%) of subjects achieving treatment success	329 (73.4)	282 (63.4)
95% confidence limits	(69.3, 77.5)	(58.9, 67.8)
P-value for treatment difference (Fisher's exact test)	0.002	

(Source: Table 5 from the sponsor's study report, the reviewer has verified the numbers.)

6 APPENDICES

6.1 Central Reader data Quality Issue – Procedure Statements

Table 11 Missing Data in the Voice Recordings on Procedure Statements – Study RAMPART

Treatment	N	Statement on the Voice Recording	Yes - a clear statement was verbalized	Missing	Missing Rate
IM Midazolam	448	IM Drug Administered	379	69	15.4%
		IV Access Obtained	243	205	45.8%
		IV Drug Administered	240	208	46.4%
		Benz. Administered	53	395	88.2%
		Seizures Terminated	311	137	30.6%
		Seizure Termination at ED Arrival	197	251	56.0%
IV Lorazepam	445	IM Drug Administered	375	70	15.7%
		IV Access Obtained	220	225	50.6%
		IV Drug Administered	272	173	38.9%
		Benz. Administered	76	369	82.9%
		Seizures Terminated	303	142	31.9%
		Seizure Termination at ED Arrival	206	239	53.7%

(Reviewer's result based on data set adcr provided by the sponsor.)

6.2 Central Reader data Quality Issue – Time Statements

Table 12 Missing Data in the Voice Recordings on Time Statements – Study RAMPART

Treatment	N	Statement on the Voice Recording	Missing	Missing Rate
IM Midazolam	448	IM Start Minutes	99	22.1%
		IM Start Seconds	99	22.1%
		IV Access Minutes	216	48.2%
		IV Access Seconds	216	48.2%
		IV Start Minutes	257	57.4%
		IV Start Seconds	257	57.4%
		Benzodiazepine Start Minutes	398	88.8%
		Benzodiazepine Start Seconds	398	88.8%
		Seizure Termination Minutes	145	32.4%
		Seizure Termination Seconds	145	32.4%
		ED Arrival Minutes	200	44.6%
		ED Arrival Seconds	200	44.6%
IV Lorazepam	445	IM Start Minutes	101	22.7%
		IM Start Seconds	102	22.9%
		IV Access Minutes	239	53.7%
		IV Access Seconds	239	53.7%
		IV Start Minutes	201	45.2%
		IV Start Seconds	202	45.4%
		Benzodiazepine Start Minutes	371	83.4%
		Benzodiazepine Start Seconds	371	83.4%
		Seizure Termination Minutes	161	36.2%
		Seizure Termination Seconds	162	36.4%
		ED Arrival Minutes	177	39.8%
		ED Arrival Seconds	178	40.0%

(Reviewer's result based on data set adcr provided by the sponsor.)

7 REFERENCES

[1] Alldredge BK1, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH (2001) A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *New England Journal of Medicine,* 2001 Dec 20; 345(25):1860.

[2] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *New England Journal of Medicine,* 2012 366(7):591-600.

[3] FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. http://www fda.gov/cder/guidance/1397fnl.pdf

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/s/

JINNAN LIU
09/12/2018

KUN JIN
09/12/2018
I concur with the review.

HSIEN MING J HUNG
09/12/2018