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RESEARCH**

APPLICATION NUMBER:

209566Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209566
Priority or Standard	Standard
Submit Date(s)	11/16/17
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PDUFA Goal Date	9/14/18
Division/Office	DNP
Reviewer Name(s)	Steven Dinsmore, DO
Review Completion Date	9/13/18
Established/Proper Name	Midazolam
(Proposed) Trade Name	Seizalam
Applicant	Meridian
Dosage Form(s)	Seizalam (midazolam injection) multiple-dose vial
Applicant Proposed Dosing Regimen(s)	Adult patients ≥ 18 years of age: 10 mg midazolam administered by intramuscular injection only [2 mL undiluted Seizalam (midazolam injection) multiple-dose vial containing 5 mg/mL].
Applicant Proposed Indication(s)/Population(s)	Seizalam is a benzodiazepine indicated for the treatment of status epilepticus in adults
Recommendation on Regulatory Action	approval
Recommended Indication(s)/Population(s)	Seizalam is indicated for the treatment of status epilepticus in adults.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class (MedDRA)
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Midazolam, a short-acting benzodiazepine, was initially approved in the United States (US) in 1985 under the trade name Versed® (NDA 018654). Midazolam is currently marketed in the US as a generic drug in IV and IM dosage forms for adults and children for sedation/anxiolysis/amnesia, induction of anesthesia prior to administration of other anesthetic agents, and for sedation of intubated and mechanically ventilated patients. Buccal midazolam is marketed in over 50 other countries worldwide for the treatment of prolonged seizures in children, but buccal midazolam is not approved in the US.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The RAMPART study of out of hospital treatment of status epilepticus is the basis for the conclusion of effectiveness. This study enrolled 1023 patients of whom 85 had 130 repeat enrollments. There were 893 patients in the ITT population of patients with 1st enrollment. There were 448 patients assigned to IM midazolam and 445 assigned to IV lorazepam treatment. Successful outcome was absence of seizure on arrival at the emergency department without use of rescue medication. In the IM midazolam treatment arm there were 329 (73.4%) patients with a successful outcome while in the IV lorazepam treatment arm there were 282 (63.4%) patients with a successful outcome. There was a significant difference ($P=0.002$) between groups tested by Fisher's exact test in this superiority analysis.

Before the initiation of the trial, the FDA specified that, for regulatory purposes, the RAMPART study must establish efficacy based on a superiority analysis. There is insufficient data on lorazepam efficacy in status epilepticus to set a non-inferiority margin. Therefore, a superiority approach to demonstrate significant separation from lorazepam is needed to assure efficacy.

(b) (4)

Evidence of effectiveness for IM midazolam to be delivered via manual injection from a multiuse vial based on the positive result of the single multicenter study described above and a bridge from midazolam Autoinjector drug product to the listed drug Versed. The investigational midazolam autoinjector drug product is Q1/Q2 similar in formulation composites to the listed drug Versed and Versed is Q1/Q2 the same as the proposed manual IM injection. A subsequent bridge of the PK properties of the manual injection of Versed to the Autoinjector drug product

is established by a literature-based PK study.

The study of IM midazolam autoinjector is interpreted in the context of a body of knowledge and experience in the use of benzodiazepines for the treatment of early status epilepticus. As identified in the 2016 American Epilepsy Society (AES) guidelines, IM midazolam, IV lorazepam or IV diazepam is the initial therapy of choice (Level A evidence) for treatment of status epilepticus in the initial 5 to 20 minutes of onset.¹ The RAMPART study submitted in this application was developed in the context of the emerging therapeutic directions for early status epilepticus. The study established superiority to IV lorazepam in a field trial of IM midazolam administered to patients in status epilepticus while in transit to an emergency department. The listed drug, lorazepam injection has a labeled indication for the treatment of status epilepticus.

The level of evidence provided is adequate to support the conclusion that IM midazolam is effective for the treatment of status epilepticus.

1.3. **Benefit-Risk Assessment**

¹ Glauser T, et. al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Currents*, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

Benefit-Risk Integrated Assessment

Status epilepticus (SE) is a life threatening neurologic emergency where rapid treatment may avoid neurologic injury and medical complications. SE usually occurs without warning and is therefore an event occurring where patients are not near a critical care setting. Availability of a therapeutic intervention that may be delivered rapidly and reliably is a goal for therapeutic intervention. Currently approved therapies are diazepam and lorazepam. Neither of these drugs is well suited for IM delivery due to delayed bioavailability where T_{max} following IM delivery is longer than T_{max} for IM midazolam. In addition, the sponsor argues that the injectable formulation of lorazepam requires refrigeration, making it difficult to stock on emergency response vehicles. Delay reaching therapeutic concentration after IM administration in the setting of SE is a serious limitation for diazepam and lorazepam.

IM midazolam has advantageous properties for both IM delivery and availability for out of hospital use. Compared with the Benzodiazepines currently approved for SE, the fused imidazole ring of midazolam confers improved stability and altered metabolism, making midazolam unique among the benzodiazepines. When the diazepine ring opens reversibly at pH <4, it forms a highly stable, water soluble, primary amine derivative. This physiochemical property allows it to be formulated and injected as an aqueous solution that can be stored in a non-refrigerated environment. In addition, Following IM injection, the peak serum levels of midazolam are reached within approximately 20-30 minutes, notably faster than those of diazepam or lorazepam.

There is extensive experience in the use of midazolam for anesthetic applications. The RAMPART study provides evidence of efficacy of IM midazolam for SE. This efficacy is bridged from the listed drug Versed to ANDA 75293 to the Autoinjector drug product, then bridged to manual injection via multiuse vial based on a literature based PK study.

The RAMPART study did not reveal any unexpected safety signals. Respiratory depression was seen but is a known complication of SE less ventilatory compromise was seen in healthy volunteers (studied at twice the proposed dose of IM midazolam for SE). Renal dysfunction was also identified in the study but was commensurate with the serious physiologic stress imposed by SE as well as the serious underlying co-morbidities that frequently exist in patients that experience SE. Overall the benefit risk assessment favors the benefit of acceptably rapid response and reliable deliver that IM midazolam allows without any clear new safety signal identified with the use of this benzodiazepine.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Status epilepticus is a life-threatening condition - Time based threat to neuronal survival - Metabolic, respiratory and hemodynamic complications accrue with increased duration of the status epilepticus episode	Early effective treatment reduces the threat of immediate medical complications and long term sequelae.
Current Treatment Options	- IV lorazepam - IV diazepam - Both may be delivered IM but this is not recommended due to the relatively slow absorption after IM injection.	Benzodiazepine treatment for early status epilepticus is standard of practice. Optimal delivery methods are needed for all medical situations, including out of hospital events.
Benefit	- IM midazolam is absorbed rapidly after IM injection - IM midazolam may be stored at room temperature - Midazolam becomes lipophilic after systemic absorption, favorable for CNS penetration	IM midazolam allows effective early phase status epilepticus treatment to be extended to the out-of-hospital EMS environment or other situations where IV access is not rapidly available.
Risk and Risk Management	- The safety risks of benzodiazepines are well known - Risks include sedation, respiratory depression - No new safety signals for midazolam delivered by IM autoinjector were identified in the study - Management of known benzodiazepine risks is inherent to the capabilities of out-of-hospital EMS	No new safety signals were established in review of the RAMPART or MRP safety data. Known risks of midazolam can be effectively managed in the critical care environment / emergency medical environment where status epilepticus must be treated.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

Analysis of Condition

Status epilepticus (SE) is a medical emergency exemplified by continuous tonic-clonic seizure activity lasting for five or more minutes or a series of seizures with no recovery between them. The incidence of SE varies from 10 to 61 per 100,000 population each year. The frequency of SE is higher in children and the aged population, and the overall SE-related mortality is ~20%. SE can occur from multiple causes, including head injury, febrile seizures, stroke, brain infections, sleep deprivation, withdrawal from alcohol and drugs of abuse, or pre-existing conditions, such as brain tumor, congenital malformations, and Alzheimer's disease.²

The operational definition of status epilepticus (SE) describes an abnormally prolonged state of self-perpetuating seizure activity.³ The International League Against Epilepsy (ILAE) recently established a new definition of SE, as follows:

"Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1). It is a condition, which can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizure."⁴

The target seizure activity of the RAMPART study that assessed efficacy of midazolam for status epilepticus was "continuous or repeated convulsive seizure activity of more than 5 minutes" This inclusion criteria is in alignment with the ILAE definition of t_1 for generalized convulsive status epilepticus. For generalized convulsive status epilepticus (CSE), t_1 is estimated to be 5 min, and t_2 30 min. Neuronal injury results from oxidative stress due to sustained energy

² Castro OW, Upadhyia D, Kodali M, Shetty AK. Resveratrol for Easing Status Epilepticus Induced Brain Injury, Inflammation, Epileptogenesis, and Cognitive and Memory Dysfunction-Are We There Yet? *Frontiers in Neurology* 2017;8.

³ Grover EH, Nazzari Y, Hirsch LJ. Treatment of Convulsive Status Epilepticus. *Current Treatment Options in Neurology* 2016;18.

⁴ Trinka E et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56D10]:1515–23

demands and may lead to cognitive sequelae. Indeed, significant numbers of SE-survivors display morbidity characterized by cognitive, memory, and mood dysfunction with an enhanced risk for developing chronic temporal lobe epilepsy (TLE).⁵ Systemic complications also result from status epilepticus. Sustained convulsive SE causes profound physiologic derangements which occur in order to compensate for a high metabolic demand. Catecholamine release disturbs the cardiovascular function by increasing the blood pressure, heart rate, and cardiac output. The pressures in the pulmonary circulation and left atrium also rise, while the threshold for cardiac arrhythmias decreases.

Early phase successful treatment is necessary to reduce morbidity and mortality associated with status epilepticus.⁶

The hyperadrenergic state also causes hyperglycemia, demargination of neutrophils, and hyperpyrexia, and these are perpetuated by sustained muscle contraction. While hyperglycemia is usually transient and well tolerated, hyperpyrexia warrants aggressive medical intervention because it is associated with the release of proconvulsant cytokines, neuropathological sequelae, and increased mortality. After approximately after 30 min of persistent seizures, compensatory mechanisms are insufficient to maintain cellular homeostasis and irreversible neuronal injury occurs.⁷

2.2. Analysis of Current Treatment Options

Table 1 Approved Treatments for Status Epilepticus

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
Diazepam	"Diazepam is a useful adjunct in status	1966	IM or IV	In an out of hospital treatment trial in 2001 42.6% of	Poor bioavailability IM	"Diazepam is a useful adjunct in status epilepticus and

⁵ Castro OW, Upadhy D, Kodali M, Shetty AK. Resveratrol for Easing Status Epilepticus Induced Brain Injury, Inflammation, Epileptogenesis, and Cognitive and Memory Dysfunction-Are We There Yet? *Frontiers in Neurology* 2017;8.

⁶ Bauerschmidt A, et. al. Advancements in the critical care management of status epilepticus. *Curr Opin Crit Care* 2017, 23:122–127. DOI:10.1097/MCC.0000000000000392

⁷ Hawkes MA, Hocker SE. Systemic Complications Following Status Epilepticus. *Current Neurology and Neuroscience Reports* 2018;18.

	epilepticus and severe recurrent convulsive seizures”			patients had resolution of SE		severe recurrent convulsive seizures”
lorazepam	“ATIVAN Injection is indicated for the treatment of status epilepticus ”	1980	IM or IV	In an out of hospital treatment trial in 2001 59.1% of patients had resolution of SE	“ATIVAN Injection is indicated for the treatment of status epilepticus”	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This 505(b)(2) application relies on the FDA’s findings of safety and/or effectiveness for the listed drug, the listed drug, and other data from the published literature. [Table 2](#) identifies the sources of information essential to the approval of Midazolam Multi-Use Vials for IM manual injection

Table 2 List of Prior Findings of Safety and Effectiveness by FDA and Other Data to Support This 505(b)(2) Application

Source of Information	Information Provided
1. Published literature	Comparative bioavailability, Request for Biowaiver; literature review of safety and efficacy
2. NDA 0186654 “Versed Injection”	Comparative bioavailability and previous findings of safety.
3. ANDA 075293	Chemistry, manufacturing, and controls, and previous findings of safety

Midazolam was approved as Versed in 1985 and currently has indications for the following;

- intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;
- intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy,

coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;

- intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);
- continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

3.2. Summary of Presubmission/Submission Regulatory Activity

The initial submission of this NDA on 11/16/17 contained a Statistical Analysis Plan (SAP) dated October 21, 2013 where the primary outcome was analyzed using a non-inferiority approach. A amendment of this earlier SAP was requested by the FDA on 1/17/18 to describe modifications to the primary statistical analysis that were performed on the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study raw data in support of a regulatory submission. This addendum is based on a longstanding agreement with the FDA to use a prespecified superiority analysis as the primary analysis for regulatory purposes

(b) (4)

3.3. Foreign Regulatory Actions and Marketing History

Midazolam for IM injection for the treatment of seizures or status epilepticus is not approved in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A clinical site inspection request was submitted to OSI. The clinical sites were chosen primarily based on high subject enrollment and prior inspectional history. The site selection information is presented in the [Data Quality and Integrity](#) Section of Section 6.1.2 Study Results

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The Clinical Inspection Summary concludes the following in Section I, Overall Assessment of Findings and Recommendations:

“The clinical sites of Drs. Hemphill and Welch were inspected in support of this NDA. In general, based on the inspections of the two clinical sites, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication although a regulatory violation was noted at Dr. Hemphill’s site (primarily due to discrepancies with study drug accountability). The final compliance classification of the inspection of Dr. Hemphill was Voluntary Action Indicated (VAI) and for that of Dr. Welch was No Action Indicated (NAI).

Of note, at both sites, subjects were enrolled multiple times (as permitted by protocol), each time receiving a different subject number. We recommend that the review division ensure that the statistical plan was followed, which stated that only the first enrollment is used in the efficacy analysis.

Audio recordings were reviewed at the clinical sites and were difficult to decipher. Data listings reviewed for Site #5 (Dr. Welch) indicate that the statement of whether a seizure had terminated was clearly verbalized on the audio recording for only 64% of subjects, for the remaining subjects the statement was unclear, absent, or no data was available in the listing. We recommend that the review division consider the amount of missing data in the evaluation of key secondary efficacy measures obtained from these audio recordings.”

Reviewer Comment: The issues identified in by the OSI Clinical Site Inspection are addressed in [section 6.1.2 Data Quality and Integrity](#). Reviewer examination of case report forms and related datasets does not identify any findings that challenge the study integrity.

4.2. **Product Quality**

Review not posted at time of this writing

4.3. **Clinical Microbiology**

N/A

4.4. **Nonclinical Pharmacology/Toxicology**

The applicant proposes to address the nonclinical requirements for approval by referencing the nonclinical studies from the listed drug Ativan and the RLD Hospira IM midazolam. The adequacy of the nonclinical studies will be addressed by the non-clinical review.

4.5. Clinical Pharmacology

Bridge from the LD drug Versed to IM midazolam for manual injection from multiuse vials, .

The Reference Listed Drug (RLD) for midazolam is Versed® Injection (NDA 018654), for which the Food and Drug Administration's (FDA's) prior findings for safety were made. Versed Injection has been discontinued (not due to reasons of safety or effectiveness), and the reference standard for midazolam has been defined as Midazolam Injection, USP (ANDA 075293) (vial, 50 mg/10 mL) and is listed as the reference standard in the Orange Book. The Midazolam Injection, USP (ANDA 075293) (vial, 50 mg/10 mL) is referred to as Midazolam Injection, USP (ANDA 075293). Midazolam Injection, USP (ANDA 075293) is the intended product formulation to be used in this NDA (209566) submission.

Both the Midazolam IM Auto-Injectors (Investigational Products) and the Midazolam Multi-Use Vials for IM manual injection contain the same active and inactive ingredients in the same concentrations as the approved drug products (Versed Injection [NDA 018654] and Midazolam Injection, USP [ANDA 075293]).

The sponsors bridge of the clinical safety, efficacy, and PK data from the Midazolam IM Auto-Injectors (Investigational Products) to the intended product formulation (Midazolam Injection, USP [ANDA 075293]) is based upon comparison of data from 5 PK studies using the Midazolam IM Auto-Injectors to PK data from literature-based studies using IM manual injections.

The Biopharmaceutics review team concludes that:

The bridge to Versed® was established based on the following comparisons (in particular, #1 and #2):

1. Manually injected Versed® was used in one literature-based PK study (Wermeling 2006).⁸ The midazolam PK results (C_{max} , AUCinf, and T_{max}) from this PK study were deemed comparable with those from the investigational Midazolam Auto-Injector drug product tested in status epilepticus patients (INDs 068432 and 102540). This comparison established the bridging to Versed® with respect to PK exposure and mode/manner of intramuscular injection. [Results confirmed by OCP reviewer]
2. Investigational Midazolam Auto-Injector drug product is Q1/Q2 similar in formulation compositions (i.e., minor differences were deemed clinically insignificant) to Versed® and

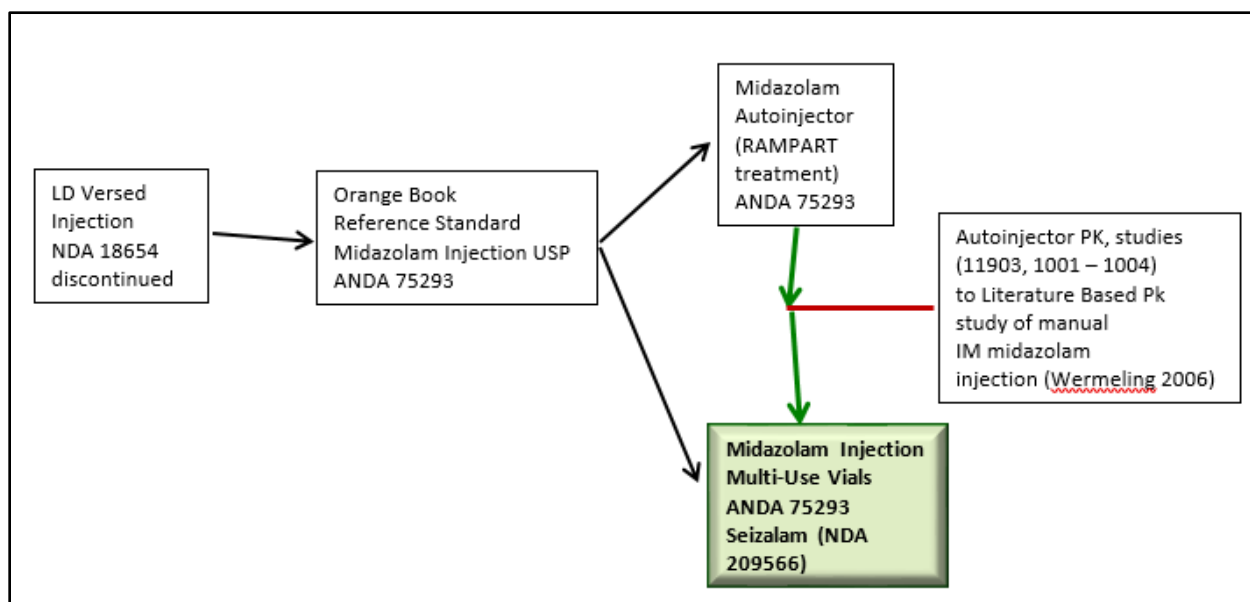
⁸ Wermeling DP, et.al. Pharmacokinetics and Pharmacodynamics of a New Intranasal Midazolam Formulation in Healthy Volunteers. *Anesth Analg* 2006;103:344 –9

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Versed® is Q1/Q2 the same as the proposed Manual IM injection.

3. The Applicant compared PK data following midazolam manual injection (formulation compositions unknown and maybe different) from 3 other literature-based PK studies with PK data from investigational Midazolam Auto-Injector. [OCP reviewer was consulted]

Figure 1 Graphic Presentation of the Continuity from Original RLD (Versed) to IM midazolam form Manual Injection



4.6. Devices and Companion Diagnostic Issues

4.7. Consumer Study Reviews

None performed

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 3 Table of Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
RAMPART Rapid Anticonvulsant Medication Prior to Arrival Trial		Phase 3 double-blind, double dummy, randomized, superiority study comparing the efficacy of IM midazolam by autoinjector to IV lorazepam in the pre-hospital setting for termination of status epilepticus.	Single IM dose of investigational product or IV dose of comparator	Efficacy was assessed by the proportion of subjects with termination of clinically evident seizure determined at arrival in the emergency department after a single dose of study drug and without use of rescue medication.	Midazolam IM Auto-Injector (Investigational Product) 10 mg/2 mL or 5 mg/mL Lorazepam 4 mg or 2 mg Treatment of either: IM midazolam injection + IV placebo, or IM placebo injection + IV lorazepam	1023 Enrollments	Adult and pediatric patients with continuing seizure activity after EMS arrival and meeting all other inclusion and exclusion criteria were enrolled in this trial.	17 Hubs 79 Hospitals US Study
<i>Studies to Support Safety</i>								
Medical Records Project		Provide Patient safety information following the RAMPART trial endpoint of determination of seizure activity upon arrival in the emergency department	See RAMPART	Review the RAMPART clinical study medical records to identify and extract pre-specified data including all deaths, safety events, serious safety events, safety events of interest (respiratory depression and acute renal failure), medical history, and prior and concomitant medications; and Create a separate	Retrospective collection and analysis of pre-specified information from the medical records of subjects who participated in the Phase 3 RAMPART clinical study	See RAMPART	See RAMPART	See RAMPART

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				comprehensive database to enable analyses of the extracted data for inclusion in New Drug Applications and other regulatory submissions, as required.				
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>								
11903		Open label dose escalation	Midazolam IM Auto-Injector (Investigational Product) 10 mg/2 mL or 5 mg/mL Target doses based upon subject weight: 0.10, 0.18, 0.25, 0.33, 0.40, or 0.49 mg/kg, with fixed total dosages administered as 5, 10, 15, 20, 25, or 30mg IM injection in vastus lateralis muscle Single-dose	Primary: To determine the dose linearity and PK of midazolam IM, and To determine the safety profile of midazolam IM administered using an auto-injector at the dose levels selected. Secondary: To assess incidents of respiratory depression, and To assess injection site responses.	Single event of dosing,	39	Healthy male and female volunteers	Single center
K643-08-1001		2-way, randomized sequence, open-label, crossover	Midazolam IM Auto-Injector (Investigational Product) 10 mg/2 mL Treatment A: 2 x 10 mg auto-injectors	Primary: <u>Primary:</u> To assess and compare the PK parameters for 2 midazolam dosing regimens	Total duration: study of 6 days with End of study day 6 assessments.	24	Healthy male and female volunteers	Single center

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			administered <1 min apart Treatment B: 2 x 10 mg auto-injectors administered 10 min apart IM injection in vastus lateralis muscle 2 treatments with 1-day period between treatments	<u>Secondary:</u> To compare the PK parameters of the active metabolite, 1-hydroxymidazolam, for both midazolam dosing regimens, and To assess and compare the two dosing regimens above with respect to: • Occurrences of respiratory Depression • Injection site reactions, • Other AEs, and • Changes in vital signs, physical examination findings, ECG findings, • clinical chemistry, hematology, and • urinalysis				
K643-08-1002		2-way, randomized sequence, open-label, crossover	Midazolam IM Auto-Injector (Investigational Product) 10 mg/2 mL AtroPen® (atropine injection) Auto-Injector 2.0 mg	<u>Primary:</u> To assess overall safety and compare the PK parameters for midazolam 2 x 10 mg auto-injectors, with injections separated by <1 min to the PK	Total duration: study of 6 days with End of study day 6 assessments.	24	Healthy male and female volunteers	Single Center

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			Treatment A: Midazolam 2 x 10 mg auto-injectors administered <1 min apart Treatment B: Atropine 2.0 mg auto-injector followed 10 min later by midazolam 2 x 10 mg auto-injectors administered <1 min apart IM injection in vastus lateralis muscle 2 treatments with 1-day period between treatments	parameters for midazolam 2 x 10 mg auto-injectors, with injections separated by <1 min and preceded by atropine sulfate (2.0 mg; 1.67 mg atropine base) administered by auto-injector. <u>Secondary:</u> To determine 1-hydroxymidazolam and atropine PK parameters when atropine was co-administered with midazolam, and To assess and compare midazolam alone to midazolam preceded by atropine with respect to: Occurrences of respiratory Depression Injection site reactions, Other AEs, and Changes in vital signs, physical examination findings, ECG findings, clinical chemistry, hematology, and urinalysis				

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
K643-08-1003		2-way, randomized sequence, open-label, crossover	Midazolam IM Auto-Injector (Investigational Product) 10 mg/2 mL ATNAA Auto-Injector (atropine 2.1 mg/0.7 mL and 2-PAM 600 mg/2.0 mL injection) Treatment A: Midazolam 2 x 10 mg auto-injectors administered <1 min apart Treatment B: Atropine (2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL), combined in a single auto-injector, followed 10 min later by 2 x 10 mg midazolam auto-injectors administered <1 min apart IM injection in vastus lateralis muscle 2 treatments with 1-day period between treatments	<u>Primary:</u> To assess overall safety and compare the PK parameters for midazolam 2 x 10 mg auto-injectors, with injections separated by <1 min when used alone to midazolam that is preceded by atropine (2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL) using a single auto-injector. <u>Secondary:</u> To determine 1-hydroxymidazolam, atropine, and 2-PAM PK parameters when co-administered with midazolam, and To assess and compare midazolam alone to midazolam preceded by atropine/2-PAM with respect to: Occurrences of respiratory Depression Injection site reactions, Other AEs, and Changes in vital signs,	Total duration: study of 6 days with End of study day 6 assessments.	24	Healthy male and female volunteers	Single Center

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				physical examination findings, ECG findings, clinical chemistry, hematology, and urinalysis				
K643-08-1004		2-way, randomized sequence, open-label, crossover	Midazolam IM Auto-Injector (Investigational Product) 10 mg/2 mL Pyridostigmine bromide 30 mg tablet ATNAA Auto-Injector (atropine 2.1 mg/0.7 mL and 2-PAM 600 mg/2.0 mL injection) Treatment A: Midazolam 2 x 10 mg auto-injectors administered <1 min apart Treatment B: Oral pyridostigmine (30 mg) followed 120 min later by atropine (2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL) by auto-injector, followed 10 min later by midazolam 2 x 10 mg auto-injectors administered <1 min apart	<u>Primary:</u> To assess safety and compare the PK parameters for midazolam 2 x 10 mg auto-injectors, with injections separated by <1 min when used alone to midazolam that is preceded by oral pyridostigmine (30 mg), atropine (2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL) by auto-injector. <u>Secondary:</u> To determine 1-hydroxymidazolam PK parameters, and atropine and 2-PAM PK parameters when co-administered with midazolam, and To assess and compare midazolam alone to midazolam preceded by pyridostigmine and atropine/2-PAM with respect to:	Total duration: study of 6 days with End of study day 6 assessments.	24	Healthy male and female volunteers	Single Center

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			IM injection in vastus lateralis muscle 2 treatments with 1- day period between treatments	Occurrences of respiratory Depression Injection site reactions, Other AEs, and Changes in vital signs, physical examination findings, ECG findings, clinical chemistry, hematology, and urinalysis				
K643-08- 1005		Open label single arm	Midazolam IM Auto- Injector (Investigational Product) 10 mg/2 mL 2 x 10 mg auto- injections administered <1 min apart IM injection in vastus lateralis muscle Single dose (as 2 autoinjectors)	<u>Primary:</u> To evaluate the safety of IM midazolam administered using an auto-injector with respect to: Occurrences of respiratory Depression Injection site reactions, Other AEs, and Changes in vital signs, physical examination findings, ECG findings, clinical chemistry, hematology, and urinalysis	3 Day CRU admission, Single dose followed by 24 and 48-hour post-dose assessment in the CRU. Return to CRU for assessment on day 8 with telephone follow up assessment on day 30.	250	Healthy male and female volunteers	Two Study Centers

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5.2. Review Strategy

Safety

RAMPART Study and Medical Records Project (MRP)

Safety data is available from the RAMPART study and the Medical Records Project (MRP). The MRP was designed to expand the safety information beyond the RAMPART case report forms to patient medical record safety data. This project provides additional safety information on the subset of patients from the RAMPART study who were admitted to the hospital after arrival at the emergency department. These two datasets will provide safety data on the use of IM midazolam, with autoinjector as delivery mechanism, in the process of patient care in the field as well as follow up safety data on patients whose status epilepticus event resulted in an inpatient admission. The safety data will be examined for new safety signals from this context of use. Also for safety issues in IM midazolam that may counter balance the positive efficacy over IV lorazepam. Safety issues of special interest in this product use context are respiratory compromise and renal dysfunction.

The RAMPART safety data will inform the overall use of IM midazolam in all enrolled patients from contact to arrival at the emergency department. A broad examination of safety in the 1st phase of treatment will be performed on deaths SAEs and TEAEs as well as the capture of the safety issues of special interest, respiratory compromise and renal dysfunction, that occur up to the point of study endpoint adjudication. The MRP safety data will be examined to assess the outcome of the patient subset that had medical status requiring admission to the hospital, rather than discharge from the emergency department after initial therapy as well as additional data from medical charts available on ED discharged patients. The set of SAEs and TEAEs from the MRP will be examined to determine if there are specific safety signal that are associated with those patients who had a more severe course of status epilepticus.

Study 1005

Study 1005 was a single arm open label study of 250 healthy adult males and female, to evaluate the safety of IM midazolam delivered as two IM Autoinjector treatment of 10mg/2ml given less than 1 minute apart. This study provided a view of the background safety issues in a healthy population with focus on respiratory / ventilatory and renal safety events. This large safety dataset will act a comparator to identify signals that may be unique to the study population.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. RAMPART Study

6.1.1. Study Design

Overview and Objective

The RAMPART study was a double-blind, randomized study to evaluate the efficacy of IM midazolam versus IV lorazepam in the prehospital treatment of *status epilepticus* by paramedics. The primary objective of the study, that was prespecified for regulatory purposes, was to determine if the efficacy of IM midazolam was superior to IV lorazepam as assessed by the proportion of subjects with termination of seizures at arrival to the emergency department after a single dose of study drug and without rescue medication. A secondary objective of the study was to compare the therapeutic rapidity of IM midazolam versus IV lorazepam by measuring the time intervals from paramedic arrival to termination of seizure and from initiation of treatment to termination of seizure. Additional secondary objectives included comparing the effects of IM midazolam and IV lorazepam on the frequency of acute endotracheal intubation, frequency of seizure recurrence, and frequency and duration of hospital stay and intensive care unit (ICU) admission.

Trial Design

This was a double-blind, double-dummy, randomized, superiority study of the efficacy of IM midazolam by auto-injector versus IV lorazepam in the pre-hospital treatment of status epilepticus by paramedics. Adult and pediatric subjects who had ongoing seizure activity after arrival of EMS, and who met all inclusion and exclusion criteria, were enrolled and randomized in this study

When paramedics arrived at the scene, they rapidly performed an initial assessment and stabilized subjects who were in status epilepticus, according to their local EMS protocols. All subjects received both an IM and an IV injection: IM midazolam by auto-injector followed by IV placebo or IM placebo by auto-injector followed by IV lorazepam.

Active study drug was given in dose tiers assigned based not on randomization, but on subject weight estimates. For IM midazolam, the high dose was 10 mg and the low dose was 5 mg. For IV lorazepam, the high dose was 4 mg and the low dose was 2 mg. Adults and those children

estimated to be ≥ 40 kg received the high dose of study drug (i.e., 10 mg IM midazolam followed by IV placebo or IM placebo followed by 4 mg IV lorazepam). Children estimated to be ≥ 13 kg but < 40 kg received the low dose (i.e., 5 mg IM midazolam followed by IV placebo or IM placebo followed by 2 mg IV lorazepam). The weight of children was estimated from their length using a length-based weight-estimation tape which was included in each study box.

Study Inclusion and Exclusion Criteria

Inclusion Criteria

- Paramedics or reliable witnesses verified continuous or repeated convulsive seizure activity of more than 5 minutes, or subject did not regain consciousness (operationally defined as meaningful speech or obeying commands) between seizures;
- Subject was still seizing on paramedic arrival; or if not, subject was unresponsive on paramedic arrival and had a qualifying generalized seizure without regaining consciousness. Subjects must have been convulsing at the time of treatment to be enrolled;
- Estimated weight ≥ 13 kg; and
- Subject could be transported to a RAMPART-participating hospital.

Exclusion Criteria

- Major trauma was the precipitant of the seizure;
- Hypoglycemia (glucose < 60 mg/dL);
- Known allergy to midazolam or lorazepam;
- Cardiac arrest or heart rate < 40 bpm;
- Medical alert tag marked with "RAMPART declined;"
- Prior treatment of seizure with diazepam auto-injector as part of another study;
- Known pregnancy;

- Prisoners.

Study Endpoints

Efficacy is defined as termination of clinically evident seizure determined at arrival in the Emergency Department (ED) after a single dose of study medication and without use of rescue medication. Subjects that do not stop seizing by 10 minutes after treatment administration are to be given rescue medication, and all subjects given rescue medication are coded as treatment failures even if they are no longer seizing on ED arrival.

Statistical Analysis Plan

The SAP was amended to support the clinical trial analysis that is consistent with the primary outcome based on examination for superiority rather than non-inferiority. From the inception of the study, the FDA has held the position that for regulatory purposes the RAMPART study must establish efficacy based on a superiority analysis. There is insufficient data on lorazepam efficacy in status epilepticus to set a non-inferiority margin. Therefore, a superiority approach to demonstrate significant separation from lorazepam is needed to determine efficacy. (b) (4)



To demonstrate superiority of the intramuscular (IM) midazolam compared to intravenous (IV) lorazepam, the primary outcome is analyzed within the intent-to-treat population using the well-known Z-test (two-sided) for comparing two independent proportions. The resulting difference in proportions, 95% CI (based on the Wald statistics) and corresponding p-value represents the treatment effect of IM midazolam versus IV lorazepam. A p-value for the two-sided test less than 0.05 will demonstrate the superiority of IM midazolam compared to IV lorazepam. This (superiority) analysis modifies the primary analysis of the RAMPART Revised Clinical Study Report (RAMPART Statistical Analysis Plan Addendum [21 October 2013]).

Protocol Amendments

An updated analysis of the efficacy outcome, submitted on February 7, 2018, based on superiority modifies the primary analysis of the RAMPART Revised Clinical Study Report (RAMPART Statistical Analysis Plan Addendum [21 October 2013]), as discussed in [Section 3.2](#).

6.1.2. Study Results

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Compliance with Good Clinical Practices

The sponsor attests the RAMPART study “The study was conducted in accordance with the Declaration of Helsinki, with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with Good Clinical Practice Guidelines”

Financial Disclosure

[The sponsor, Meridian Medical Technologies was not a sponsor of the covered study (RAMPART). The RAMPART study was conducted by the University of Michigan through funding by the NIH. Meridian Medical Technologies did supply the autoinjectors and associated training materials. These items were also provided through NIH funding and supplied to the University. Although there is no form 3454 for this study the principle investigator for the study attests that no clinical investigators involved in the study:

1. participated in any financial arrangement whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study,
2. had proprietary interest in the tested product,
3. had significant equity interest in the sponsor of the study during the time of the study and for 1 year following completion of the study,
4. received significant payments of other sorts as defined in 21 CFR 54.2 (f).

Based on the Guidance document “Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators”, question E.7 this financial disclosure appears adequate due to the isolation of the sponsor from the University of Michigan because all study expense is provided by the National Institutes of Health.

Patient Disposition

There were 262 investigators from 79 participating hospitals grouped into 17 study hubs. From these participating sites, there were 893 unique patient enrollments. There were 85 patients who contributed 130 re-enrollments to yield 1023 total enrollments, see [Table 4](#).

Unique Patient Enrollment by Study Arm (n=893)

- 448 subjects in the IM midazolam group (62 subjects were randomized to receive 5 mg IM midazolam and 386 subjects were randomized to receive 10 mg IM midazolam)
- 445 subjects in the IV lorazepam group (59 subjects were randomized to receive 2 mg IV lorazepam and 386 subjects were randomized to receive 4 mg IV lorazepam).

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Re-enrollment (n= 130)

- 66 re-enrollments to the IM midazolam group (4 subject re-enrollments to 5 mg IM midazolam and 62 subject re-enrollments to 10 mg IM midazolam)
- 64 re-enrollments to the IV lorazepam group (3 subject re-enrollments to 2 mg IV lorazepam and 61 subject re-enrollments to 4 mg IV lorazepam).

Intraosseous Administration

Of the 893 subjects in the ITT population, 11 received the IV study drug via intraosseous administration. . Four of these subjects were in the IM midazolam treatment arm where the dummy (inactive) IV lorazepam treatment was administered to the intraosseous compartment. The remaining 7 IV lorazepam had their active treatment delivered into the intraosseous compartment. The protocol did permit IV study drug to be administered via the intraosseous route.

Among the re-enrollment entries (130 patients), 3 were subjects who received the IV study drug via intraosseous administration (1 subject in the IM midazolam group and 2 subjects in the IV lorazepam group).

No Treatment Administration

In this emergency treatment setting, it was possible to be enrolled and randomized in the study and subsequently fail to receive treatment (active or placebo) due to incorrect autoinjector use or malfunction or inability to obtain IV access or if seizure stopped before IV access.

- Based on the method of verbal statements made by paramedics and captured on the voice recorder, 172 subjects were considered to have not received IM injection (84 subjects in the IM midazolam group and 88 subjects in the IV lorazepam group) and 525 subjects were considered to have not received IV injection (295 subjects in the IM midazolam group and 230 subjects in the IV lorazepam group).
- Based on the method of study team notification by paramedics upon emergency department arrival, 4 subjects (all in the IM midazolam group) were considered to have not received IM injection and 425 subjects were considered to have not received IV injection (253 subjects in the IM midazolam group and 172 subjects in the IV lorazepam group). Of those subjects who, based on the method of study team notification, were considered to have not received IV injection, the following reasons were provided:
 - Seizures stopped prior to IV start (197 subjects in the IM midazolam group and

- 109 subjects in the IV lorazepam group);
- o Medics unable to start IV prior to emergency department arrival (41 subjects in the IM midazolam group and 49 subjects in the IV lorazepam group);
 - o Other (15 subjects in the IM midazolam group and 14 subjects in the IV lorazepam group).

Study Discharge; End of Study

After receiving study drug, subjects were followed in the study for up to 90 days while they remained in the hospital. One (0.1%) subject was hospitalized and followed for the full 90 days. Reasons for ending the study included the following:

- hospital discharge (563 [55.0%] subjects), discharged from emergency department without hospital admission (382 [37.3%] subjects), withdrew consent (23 [2.2%] subjects), death (19 [1.9%] subjects), lost to follow-up (1 [0.1%] subject), and other reasons (34 [3.3%] subjects).
- Note that 1 subject (Subject (b) (6)) in the 4 mg IV lorazepam group died from sepsis; however, the reason for 'end of study' provided on the End of Study CRF was listed as 'consent withdrawn/decline for other reasons' rather than 'death,' as consent was withdrawn by family members near the time of death. Therefore, this subject death contributed to the total of 23 subjects who withdrew consent.

Table 4 Summary of RAMPART Subject Disposition (from sponsor table 2, RAMPART Clinical Study Report)

Category	IM Midazolam			IV Lorazepam			Total n (%)
	Low Dose 5 mg n (%)	High Dose 10 mg n (%)	Total n (%)	Low Dose 2 mg n (%)	High Dose 4 mg n (%)	Total n (%)	
Enrollments/ randomizations	66 (100.0)	448 (100.0)	514 (100.0)	62 (100.0)	447 (100.0)	509 (100.0)	1023 (100.0)
Re-enrollments	4 (6.1)	62 (13.8)	66 (12.8)	3 (4.8)	61 (13.6)	64 (12.6)	130 (12.7)
Included in ITT Population [1]	62 (93.9)	386 (86.2)	448 (87.2)	59 (95.2)	386 (86.4)	445 (87.4)	893 (87.3)
Did not receive IM injection per ED [2]	0 (0.0)	4 (0.9)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Did not receive IV injection per ED [2]	37 (56.1)	216 (48.2)	253 (49.2)	17 (27.4)	155 (34.7)	172 (33.8)	425 (41.5)
Seizure stopped prior to IV start	27 (40.9)	170 (37.9)	197 (38.3)	11 (17.7)	98 (21.9)	109 (21.4)	306 (29.9)
Medics unable to start IV prior to ED arrival	6 (9.1)	35 (7.8)	41 (8.0)	4 (6.5)	45 (10.1)	49 (9.6)	90 (8.8)
Other	4 (6.1)	11 (2.5)	15 (2.9)	2 (3.2)	12 (2.7)	14 (2.8)	29 (2.8)
Did not receive IM injection per CR [3]	8 (12.1)	76 (17.0)	84 (16.3)	9 (14.5)	79 (17.7)	88 (17.3)	172 (16.8)

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Category	IM Midazolam			IV Lorazepam			Total n (%)
	Low Dose 5 mg n (%)	High Dose 10 mg n (%)	Total n (%)	Low Dose 2 mg n (%)	High Dose 4 mg n (%)	Total n (%)	
Did not receive IV injection per CR [3]	40 (60.6)	255 (56.9)	295 (57.4)	25 (40.3)	205 (45.9)	230 (45.2)	525 (51.3)
Included in Per-Protocol Population [4]	41 (62.1)	321 (71.7)	362 (70.4)	43 (69.4)	327 (73.2)	370 (72.7)	732 (71.6)
Reason for end of study							
Discharged from emergency department without hospital admission	31 (47.0)	178 (39.7)	209 (40.7)	22 (35.5)	151 (33.8)	173 (34.0)	382 (37.3)
Hospital discharge	29 (43.9)	234 (52.2)	263 (51.2)	34 (54.8)	266 (59.5)	300 (58.9)	563 (55.0)
Hospital admission for 90 days	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Death	1 (1.5)	10 (2.2)	11 (2.1)	0 (0.0)	8 (1.8)	8 (1.6)	19 (1.9)
Consent withdrawn /declined due to an adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn/declined for other reason	0 (0.0)	12 (2.7)	12 (2.3)	1 (1.6)	10 (2.2)	11 (2.2)	23 (2.2)
Lost to follow up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)
Other	5 (7.6)	13 (2.9)	18 (3.5)	5 (8.1)	11 (2.5)	16 (3.1)	34 (3.3)
Total Deaths	1 (1.5)	10 (2.2)	11 (2.1)	0 (0.0)	9 (2.0) *	9 (1.8) *	20 (2.0) *

Doses were not randomly assigned. Children estimated to be ≥ 13 kg but < 40 kg received the low dose. Adults and those children estimated to be ≥ 40 kg received the high dose.

* One subject (Subject (b) (6)) in the 4 mg IV lorazepam group died from sepsis; however, the reason for 'end of study' provided on the End of Study CRF was listed as 'consent withdrawn/decline for other reasons' rather than 'death.'

1. The ITT Population included all subjects who were randomized and had an auto-injector applied to the thigh, regardless of which treatment (active drug or placebo) was assigned. Randomization was defined as occurring at the time the auto-injector was applied to the subject, regardless of whether the IM treatment was successfully administered. Subjects were not excluded if they did not receive active treatment. The second/subsequent enrollments for subjects who were repeat enrollers were excluded from the ITT Population (n = 85 subjects who account for 130 re-enrollments).

2. Based on study team notification by paramedics upon ED arrival.

3. Based on CR (central reader) review of EMS voice recordings. Includes all subjects for whom no statement was verbalized that drug was received.

4. The Per-Protocol Population included ITT subjects who did not have the following protocol violations: eligibility violations, incorrect dose of study drug, or incorrect administration of study drug. Subjects were not excluded if they did not receive active treatment.

CR = central reader; CRF = Case Report Form; ED = emergency department; EMS = Emergency Medical Services; IM = intramuscular; ITT = Intent-to-Treat; IV = intravenous.

Protocol Violations/Deviations

There were 214 protocol deviations that included 64 unique violation entries. The IM midazolam and IV lorazepam treatment arms. From among these there were 112 entries in the IM midazolam treatment arm and 102 in the IV lorazepam treatment arm, see [Table 5](#). The protocol violations are examined for similar syntax that would allow grouping of violation entries. Fifty eight of the 64 initial violation entries are grouped to capture 191 of the original 214 protocol violations. The frequency of specific violations between treatment are compared. The most common entries with ≥ 5 unique occurrences in both treatment arms combined are “Study medications administered at inappropriate stage of care” (60 entries), “Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min.” (23 entries), “Autoinjector given in arm or other body part (instead of in thigh)” (15 entries), “Transport to RAMPART participating ED” (14 entries), “hypoglycemia” (8 entries), and “IV study drug administered intramuscularly” (5 entries).

From among the 191 entries captured in the 58 violation categories there were 100 in the IM midazolam treatment arm and 91 in the IV lorazepam arm. The violations were further examined to best identify entries that would result in an IM or IV treatment delivery failure. There were 11 entries that would result in an IM failure and 12 entries that would result in IV failure. Entries were also examined to identify events that would result in delivery of a low dose to a high dose tier assignment or deliver of high dose to a low dose tier assignment. This exam reveals there were 9 events that would result in a low dose to high dose assignment. Eight of these occurrences were in the IM midazolam treatment arm and 1 in the IV lorazepam arm. There was one occurrence of a high dose delivered to a low tier assignment, this occurred in a patient in the IV lorazepam treatment arm.

The nature of several of the violation entries that occurred with high frequency was unclear. These include “Study medications administered at inappropriate stage of care”, “Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min.” and “Transport to RAMPART participating ED”.

Inappropriate stage of care is very non-specific. The events of “continuous convulsive seizure....” And “Transport to RAMPART participating ED” are inclusion criteria and necessary for successful study enrollment respectively. An information request was sent to the sponsor to clarify these events. The entries for “inappropriate stage of care” may consist of several changes in sequence of administration of the study drugs (IM or IV) in relation to seizure cessation and rescue medication administration. The entries for “continuous convulsive seizure....” And “Transport to RAMPART participating ED” are events when these inclusion criteria were not met.

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Table 5 RAMPART Protocol Violation Entries

Protocol Violation	IM Patients	IV Patients	comment	IM failure (other),	IV failure (other)	low dose to high tier subject	hypoglycemia	high dose to low tier subject
Study medications administered at inappropriate stage of care	25	35		0	0			
Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min.	14	9		0	0			
Autoinjector given in arm or other body part (instead of in thigh)	9	6		0	0			
Transport to RAMPART participating ED	6	8		0	0			
Hypoglycemia	5	3					1	
IV study drug administered intramuscularly	3	2		0	1			
Estimated weight >= 13kg	2	0						
Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min., Hypoglycemia	1	1					1	
Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min., Patient still convulsing on EMS arrival and at time of treatment	1	0						
Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min., Prisoner	1	0						
Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min., Study medications administered at inappropriate stage of care	1	1						
Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min., Wrong dose (low dose given to high dose subject), Autoinjector given in arm or other body part (instead of in thigh)	1	0		1		1		
Continuous convulsive seizures (or repeated convulsive seizure without waking up) > 5 min., Study medications administered at inappropriate stage of care Other: EMS originally dispatched for stroke like symptoms. During assessment, the patient c/o focal motor seizures starting in the upper extremities then to full tonic-clonic seizures. EMS decided to enroll the patient. It took the EMS crew 2 minutes to retrieve the RAMPART Box and begin treatment.	0	1						

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Protocol Violation	IM Patients	IV Patients	comment	IM failure (other),	IV failure (other)	low dose to high tier subject	hypoglycemia	high dose to low tier subject
EMS crew enrolled this witnessed seizure with a total seizure duration of less than 5 minutes.								
Hypoglycemia, Wrong dose (low dose given to high dose subject)	1	0				1	1	
Medical alert tag or other indicator marked with 'RAMPART declined'	1	0		1				
Other: 7 minutes between IM study medication and rescue medication.	1	0						
Other: After IM and IV study medications were given, the medics administered 10mg diazepam after 4 minutes from the time the IM study medication was given.	1	1		1				
Other: Auto injector did not appear to deploy and was pulled out. It then began to squirt medication and they restuck the patient with it. After IV was established, carpject broke and they were unable to give the IV study medication so they moved on to their routine protocol.	1	0		1				
Other: AUTOINJECTOR PREMATURELY WITHDRAWN FROM THIGH WITH SPILLING OF CONTENTS	0	1		1				
Other: Auto injector malfunctioned	1	0		1				
Other: Autoinjector needle was bent when removed. EMS stopped study at that point believing medication was not given. They returned to their protocol and gave 5mg valium.	1	0		1				
Other: Failed to give IV study med after IM even though patient was still seizing. Gave rescue drug instead.	0	1			1			
Other: Glucose level not documented on EMS record, however, verbal confirmation was obtained from EMS at time of enrollment (see paramedic call-in form) that glucose was assessed and was > 60 mg/dL.	1	0						

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Protocol Violation	IM Patients	IV Patients	comment	IM failure (other),	IV failure (other)	low dose to high tier subject	hypoglycemia	high dose to low tier subject
other: IM autoinjector not administered because pre-hospital care provider failed to remove the blue cap from the autoinjector. This was confirmed in the ambulance bay by the research team> Immediate re-education was performed.	1	0		1				
Other: Medic could not obtain IV access so therefore gave IM rescue drug instead of giving IV dose per IO.	0	1			1			
other: Medic gave IM injection but was nervous about patient continuing to seize so skipped the IV study dose and provided IV bailout instead.	0	1			1			
Other: Medic did not call investigator. Got pulled back into busy system by radio and forgot. PI saw subject in ICU 24hrs later and subject was notified of study and subsequently consented to study.	1	0						
Other: No study drug given. Per medic, while attempting to enroll pt, medic placed auto-injector against jeans and, as the needle came out it bent and dispensed the contents onto the floor.	1	0		1				
other: on call study team member not notified on patient arrival. Notification and consent process thus delayed. Study team became aware at approximately 2000 hours on 18-Oct.	1	0						
Other: Paramedic did not give IV med because IV was in Pt's foot.	1	0			1			
Other: Paramedics did not notify RAMPART study team of enrollment	1	0						
Other: Paramedics attempted multiple IVs without success The IV study solution was not administered IV. The IV Study solution was not administered IV. The IV study solution was not administered IO. Seven minutes after the IM study solution was administered the study was discontinued and the base Physician authorized a rescue dose of 2mg IM midazolam at this time.	0	1			1			

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Seizalam (midazolam IM injection)

Protocol Violation	IM Patients	IV Patients	comment	IM failure (other),	IV failure (other)	low dose to high tier subject	hypoglycemia	high dose to low tier subject
Other: paramedics reported that they were unable to get the IV syringe loaded into the carpject. The pt was not given IV study med even though she was still seizing. She was given rescue dose of versed 3mg IV.	0	1			1			
Other: paramedics failed to notify study team of enrollment. Used study box discovered on 60-day drug switch out.	1	0						
Other: Pt already had IV in place on EMS arrival	0	1						
Other: Pt did not get IV med because study drug equipment was broken	4	0			2			
Other: rescue medication given within 10-minute window after attempts at IV access failed twice.	1	0			1			
Other: Research team not notified of pt enrollment; team became aware of omission on 28-Dec-2009 and consent obtained from pt at that time.	0	1						
Other: Subject has a port-a-cath. Subject should not have been enrolled per monitor.	0	1						
Other: subject received IM, medics could not start IV, given IN rescue then IO rescue. Subject should have been given IO study drug prior to IN rescue.	0	1			1			
Other: Subject was appropriately enrolled with the purple top auto injector after being measured with the RAMPART tape. Paramedic then gained IV access and within 4 min, administered rescue drug instead of giving the IV study drug. Paramedic had no explanation for this except that she misinterpreted the study protocol. This paramedic was immediately remediated by the on-call neuro fellow who took the call and later by the EMS coordinator.	0	1						
Other: The carpject device broke when medic was pushing IV drug. Arrived to hospital prior to being able to draw the IV up and deliver with needle.	0	1			1			
Other: the IM autoinjector failed to "trigger" the needle. The medic appropriately aborted the protocol and provided local standard treatment protocol.	1	0		1				

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Seizalam (midazolam IM injection)

Protocol Violation	IM Patients	IV Patients	comment	IM failure (other),	IV failure (other)	low dose to high tier subject	hypoglycemia	high dose to low tier subject
Other: After IM and IV study medications were given, the medics administered 10mg diazepam after 4 minutes from the time the IM study medication was given.	0	1						
Patient still convulsing on EMS arrival and at time of treatment, Study medications administered at inappropriate stage of care, Autoinjector given in arm or other body part (instead of in thigh)	1	2	IV entry had similar entry without body part and stage of care					
Study medications administered at inappropriate stage of care, Autoinjector given in arm or other body part (instead of in thigh)	0	1						
Study medications administered at inappropriate stage of care Other: IM auto-injector withdrawn early- some med squirted out.	1	1		1				
transport to RAMPART participating ED	1	0						
Transport to RAMPART participating ED, Study medications administered at inappropriate stage of care	0	1						
Transport to RAMPART participating ED, Wrong dose (low dose given to high dose subject)	0	2				1		
wrong dose (low dose given to high dose subject)	1	2						1
Wrong dose (high dose given to low dose subject)	1	0				1		
Wrong dose (low dose given to high dose subject) Other: 1. Outdated ICD form was used. Subject was re consented with the correct ICD form the next morning in the	1	0				1		
Wrong dose (low dose given to high dose subject) Other: IV dose not given because study drug equipment was broken	1	0				1		
Wrong dose (low dose given to high dose subject) Other: paramedic did not try to give IV prior to rescue drug.	1	0				1		
Wrong dose (low dose given to high dose subject), Autoinjector given in arm or other body part (instead of in thigh)	1	0				1		

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Seizalam (midazolam IM injection)

Protocol Violation	IM Patients	IV Patients	comment	IM failure (other),	IV failure (other)	low dose to high tier subject	hypoglycemia	high dose to low tier subject
Wrong dose (low dose given to high dose subject), Study medications administered at inappropriate stage of care	1	2				1		
Totals	100	91		11	12	9	3	1

Reviewer Comment: The total frequency of protocol violations between the treatment arms is balanced. The frequency of the broad category of “study medications administered at inappropriate stage of care” has greater distribution in the IV lorazepam treatment arm but the difference between arms is 1.1% of the study population. The remaining high frequency categories are more closely balanced. The frequency of “low dose delivery to high dose tier” occurs eight of nine times in the IM midazolam arm. This event would likely give advantage to the IM lorazepam arm and does not influence the outcome toward a false positive IM midazolam treatment effect. Overall the profile of protocol violations does not appear to bias study outcome.

Table of Demographic Characteristics

Examination of demographic characteristics of the RAMPART study population reveal a small disproportion of male over female subjects in the total study group that carries through the IM midazolam and IV lorazepam. The total study population had 54.6% males and 45.4% females. The mean and media study population were 43.4 and 46 respectively with a minimum of 0 and maximum of 90. One patient in the dataset has a listed age of zero without an age in months entered. Distribution by age group is examined. The highest proportion of patients by age is in the $17 \leq$ to < 65 age range with the next highest proportion of patients in the $65 \leq$ range. There was a prominent 5.9% of patients in the $2 \leq$ to < 6 age range. Racial composition was predominantly Black/African American and White at 50.7% and 39% respectively. Ethnicity was predominantly Not Hispanic or Latino, see [Table 6](#).

Table 6 RAMPART Demographic Characteristics

Demographic Parameters	IM Midazolam (n= 448)		IV lorazepam (N=445)		Total (N= 893)
Unique Patient Entries	N	%	N	%	n (%)
Sex					
Male	250	55.8	238	53.5	488 (54.6)
Female	198	44.2	207	46.5	405 (45.4)
Age					
Mean years (SD)	42.7 (21.6)		44 (22.1)		43.4 (21.8)
Median (years)	46		46		46
Min, max (years)	0, 90		1, 90		0, 90
Age Group					
0 to < 2	6	1.3	2	0.4	8 (0.9)
2≤ to <6	26	5.8	27	6.1	53 (5.9)
6≤ to <12	16	3.6	20	4.5	36 (4.0)
12≤ to <17	9	2.0	7	1.6	16 (1.8)
17≤ to < 65	330	73.7	317	71.2	647 (72.5)
65 ≤	61	13.6	72	16.2	133 (14.9)
Race					
Black/African American	229	51.1	224	50.3	453 (50.7)
White	165	36.8	183	41.1	348 (39.0)
Unknown/Not Reported	25	5.6	11	2.5	36 (4.0)
More Than One Race	9	2.0	5	1.1	14 (1.6)
Asian	8	1.8	14	3.1	22 (2.5)
Other	7	1.6	2	0.4	9 (1.0)
American Indian/Alaska Native	3	0.7	5	1.1	8 (0.9)
Native Hawaiian/Other Pacific Island	2	0.4	1	0.2	3 (0.3)
Ethnicity					
Hispanic or Latino	49	10.9	57	12.8	106 (11.9)
Not Hispanic or Latino	310	69.2	290	65.2	600 (67.2)
Unknown / not reported	89	19.9	98	22.0	187 (22.0)

Reviewer Comment: there was an excess of male over female subjects in the total population with similar proportions in the IM and IV groups. Age distribution across the treatment arms was very similar. There was no large disproportion of age subgroups across the treatment arms.

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Racial distribution was balanced across the treatment arms. Overall, no notable imbalance in demographic characteristics was present across the IM midazolam and IV lorazepam treatment arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Basic Categories for underlying disease or patient characteristics were captured in RAMPART, “Acute threshold-lowering co-morbidities”, “anticonvulsant withdrawal / noncompliance”, “idiopathic or refractory breakthrough seizures from prior pathology”. The frequency of each category in both treatment arms is examined. Thirty five percent of patients in each treatment arm had no entry provided for this information. The frequency of “acute threshold-lowering co-morbidities” in the IM midazolam compared to the IV lorazepam treatment arm were 7.4% and 6.5% respectively. The frequency of “Anticonvulsant withdrawal / noncompliance” in the IM midazolam compared to the IV lorazepam treatment arms were 31% and 32% respectively with the frequency of “Idiopathic or refractory breakthrough seizures from prior pathology” was 27% in both the IM midazolam and IV lorazepam arms, . This examination reveals that background epilepsy characteristics and potential SE precipitants are equally balanced between treatment arms, [Table 7](#).

Table 7 RAMPART ITT Population, Background Epilepsy Characteristics and SE Precipitant Categories by Treatment Arm.

Precipitant-Subj Prior Epilepsy-Char	IM		IV	
	# Patients	% Patients	# Patients	% patients
No entry (not provided)	157	35.0	154	34.6
Acute threshold-lowering co-morbidities	33	7.4	29	6.5
Anticonvulsant withdrawal / noncompliance	137	30.6	141	31.7
Idiopathic or refractory breakthrough seizures from prior pathology	121	27.0	121	27.2

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance in this single dose emergency treatment study is determined by the characteristics of the treatment environment rather than individual patient compliance in longer term multiple dose studies. The use of rescue medication was protocol directed and is shown in . Concomitant medications were captured retrospectively in the MRP.

Efficacy Results – Primary Endpoint

The primary outcome was the binary outcome variable measuring whether or not 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% see [Table 8](#).

Table 8 Primary Efficacy Results

	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)
Treatment difference vs. IV lorazepam	10.07	
P-value for treatment difference (Fisher's exact test)	0.002	
No. (%) of subjects with treatment failure	119 (26.6)	163 (36.6)
Seizures not terminated, no rescue therapy given	50 (11.2)	64 (14.4)
Seizures not terminated, rescue therapy given	22 (4.9)	42 (9.4)
Seizures terminated, rescue therapy given	47 (10.5)	57 (12.8)

Data Quality and Integrity

Two site inspections were performed. The clinical sites were chosen primarily based on high subject enrollment and prior inspection history. These sites with investigator and subject enrollment are shown in [Table 9](#).

The overall inspection findings of sites (HUB) number 16 and number 5 reveal the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication although a regulatory violation was noted at site 16 (primarily due to discrepancies with study drug accountability). The final compliance classification of the inspection of site 16 was Voluntary Action Indicated (VAI) and for that of site 5 was No Action Indicated (NAI).

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Table 9 RAMPART Clinical Site Inspections

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection dates	Compliance classification
Site #16 J. Claude Hemphill III, M.D. San Francisco General Hospital ZSFGH, Bldg 1, Room 101 San Francisco, CA 94110	RAMPART Subjects: 113	11-22 May 2018	VAI = Voluntary Action Indicated, deviation(s) from regulations.
Site #5 Robert Welch, M.D. Detroit Receiving Hospital Department of Emergency Medicine 4201 St. Antoine, 6G-UHC Detroit, MD 48201	RAMPART Subjects: 178	15-21 May 2018	NAI = No Action Indicated, no deviation from regulations.

Dose Tier -Weight Discordance

In the ITT population, there were 24 patients with weight ≥ 40 kg who received low dose tier treatment, [Table 10](#). There was a larger proportion of this dose tier to weight mismatch in the IM midazolam treatment arm than in the IV lorazepam treatment arm.

Table 10 RAMPART ITT Population, Patients with Dose to Weight Mismatch Who Received Low Dose Tier with Weight ≥ 40 kg

	24 ITT Patients Received Wrong Dose Tier Based on Weight	
Treatment Arm	# Patients	% patients
IM Midazolam	14	3.13
IV Lorazepam	10	2.25

There were 7 patients in the ITT population with a weight to dose tier mismatch where the high dose tier was delivered to patient < 40 kg weight. The greater proportion of these patients were in the IV lorazepam treatment arm, [Table 11](#).

Table 11 RAMPART ITT Population, Patients with Dose to Weight Mismatch Who Received High Dose Tier with Weight < 40 kg

	7 Pts less than 40kg in dose 2 tier	
Treatment arm	# Patients	% patients
IM Midazolam	3	0.67

IV Lorazepam	4	0.90
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Reviewer Comment: The dose tier to weight mismatch in both cases of high and low dose tier mismatch favor the IV lorazepam treatment arm. The excess of IM midazolam patients who received low dose for their weight would tend to under treat SE and be in favor of lorazepam while the small excess of patients who received high dose for weight in the lorazepam treatment arm would over treat the lorazepam SE patient and be more favorable to a cessation of seizure in those lorazepam treated patients. These mismatches do not negatively affect the validity of the RAMPART study outcome.

1st Enrollment for Outcome Analysis Population (ITT)

It was noted by the inspection team that subjects were enrolled multiple times (as permitted by protocol), each time receiving a different subject number. Originally, subject numbers were assigned by the WebDCU (data capture system) and were sequential. However, at some point, all WebDCU subject numbers were changed to the subject numbers reflected in the NDA submission where the subject number assigned for the first enrollment was not sequential. This created a concern that enrollments that were not 1st study enrollments could have been included in the ITT population.

This was assessed by the clinical reviewer by examination of a repeat enrollment cross reference table provided by sponsor after an information request. Using this table the initial subject ID enrollments from the ADSL dataset are compared with the dedicated repeat enrollment table (with common identifier for initial and subsequent enrollments) and there is no mismatch. Initial enrollment IDs align between the datasets without subsequent enrollment IDs turning up as initial enrollment IDs, although they were likely derived from the same source dataset.

In the OSI Clinical inspection report the initial and subsequent enrollment ID numbers are provided for the sites under audit, number 5 and 16. The reviewer then cross checked the sponsor ADSL dataset and the separate re-enrollment table and compared these to the initial ID and subsequent ID assignments from sites # 5 and # 16 in the clinical inspection summary (page 5 & 7). Again, there is no misalignment of initial enrollment and subsequent ID numbers across all three datasets. All initial enrollment ID numbers are consistent without mixing of initial with subsequent in any datasource. In conclusion, it appears that although the method of ID number assignment changed during the study, the initial and repeat enrollment ID assignments remained partitioned. The composite cross-checked table was used to test the primary outcome result for IM midazolam and IV lorazepam. This test confirmed the 893 initial enrollment assignments and was able to reproduce the IM midazolam and IV lorazepam outcome results (IM = 73.4% success, IV = 63.4% success).

Seizure Termination ED Determination vs 1st Responder Audio Recording

An additional concern identified in the site inspection report was the frequency of audio recordings that did not capture a clearly verbalized statement that seizure had terminated. At site number 5 it was found that a clear identification by audio verbal recording that seizure had terminated was present for 64% of patients, for the remaining patients the statement was unclear, absent, or no data was available in the listing.

As follow up to this issue the sponsor ADCR dataset was examined to determine at site 5 the proportion of patients where seizure termination was not clearly identifiable. The result of this analysis revealed that in 63% of all patients (including repeat enrollment) the audio recording identified a clear verbalization of seizure termination. This agrees with the findings of the inspection team and is similar to the overall findings for this variable in the ITT population where clear audio statement of seizure termination was present in 69% of patients.

The protocol directed measure for assessment of primary outcome is as follows:

“Determination of termination of seizure upon arrival at the receiving emergency department is made by the attending emergency physician treating the subject. The determination is made clinically using best judgement based upon exam, clinical course, and testing. The attending emergency physician’s determination is collected and reported by the on-call study team member in the ED.”⁹

Although, as noted by the OSI investigator, there is not a corresponding verbal audio record of “seizure termination” for each patient the audio file is not the basis for determination of the primary outcome measure. Onsite determination by the emergency department attending physician is the entry of record for “seizure termination”. In order to check the fidelity of the SAS.xpt datasets, the seizure termination entry variable F02Q03 from the STDM “form02” ED arrival form dataset, is compared directly with the entry for question 3 of the ED arrival page of the case report form. This comparison is performed for sampling of patients from each study hub. A total of 290 case report forms were examined and the entry for question 3, ED arrival form “In the judgement of the attending emergency physician, was the subject seizing at the time of ED arrival” was recorded to check for a match with the sponsor provided STDM dataset. The reviewer found all 290 entries were in agreement between the case report form and the dataset entry.

An additional examination of the STDM and AdAM datasets was performed to determine if there were any primary outcome success entries with corresponding entries of “2” for F02Q03

⁹ Protocol Version 3.0, (18 August 2010)

and “No - the statement was unclear or absent” in the ADCR, central reader dataset. The entry 2 in F02Q03 represents “unknown” entered in the ED arrival form. If both of these entries are present, it is contrary to the possibility of a successful outcome because the ED arrival form does not contain data consistent with success and cross check with an alternate datasource from the verbal recording entry also does not yield a possible positive outcome. There were two patients identified in the ITT dataset with this combination of entries, patients (b) (6) in the IM midazolam treatment arm and (b) (6) in the IV lorazepam treatment arm. Because there is one of these contradictory entries in each treatment arm the overall study outcome would not be affected. No other discordance was found in the examination of F02Q03 (Subject seizing when ED arrival- from case report form) , verbal audio entry “SZTMEDAN’ (Seizures Terminated at ED Arrival) and “PRIMARY” (primary outcome) variables in the datasets.

Reviewer Comment: The OSI inspection report did not identify violations at study hub # 5 or # 16 that would invalidate study integrity. Reviewer examination did not identify evidence that repeat enrollments contributed to the ITT, outcome analysis population. There was also no evidence of discordance between case report form entries and corresponding dataset entries for 290 patients sampled to test fidelity of these entries. There were two patients identified with data inconsistent with declaration of a successful outcome. The ED form Q3 indicated an unknown status for seizure activity while the primary outcome was entered as success. These patients contributed one each to the IM midazolam and IV lorazepam treatment arms respectively, therefore the balance between **treatment** arms is not altered and the RAMPART study outcome is not changed.

Efficacy Results – Secondary and other relevant endpoints

The Biometrics review team reports "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."

The descriptive characteristics of the time to seizure termination and time to treatment delivery are discussed in "" shown below.

Dose/Dose Response

Dose response data is not available from RAMPART. This study had a single dose arm for each treatment with high and low tier adjustment by weight $\geq 40\text{kg}$ or $< 40\text{kg}$. Eleven percent (11.1%) of the study population was under age 12 years where the female 50th percentile for is approximately 40kg.

Durability of Response

There was no sustained treatment with study drug to provide assessment of response over time.

Persistence of Effect

Acute recurrence of seizure within 12 hours after ED arrival was evaluated. In the ITT population there were 50 (11.2%) patients in the IM midazolam treatment arm with recurrence of seizure while in the IV lorazepam arm there were 47 (10.6%) patients with a seizure recurrence. This examination reveals no clear difference in recurrence of seizure between treatment arms.¹⁰

Additional Analyses Conducted on the Individual Trial

A more rapid IM delivery may offset a more rapid rise to therapeutic exposure of an intravenous delivery route. The following analyses examined the time to IM and IV delivery and seizure termination in all patients and ITT (no repeat enrollments) populations. These analyses are derived from the adcr.xpt dataset.

Time to Treatment Delivery

Time to treatment delivery for both autoinjector (IM) and IV is examined for the total patient group including repeat enrollment patients. This patient group provides the largest sample to examine for time to treatment delivery. This examination includes both the active and dummy delivery. Overall mean and median time to treatment delivery for the IM route are 111 seconds and 77 seconds respectively while for the IV route times were 407 and 325 seconds respectively. This examination reveals the mean time to delivery using the intravenous route was almost 5 minutes (4.93 minutes) longer than time to autoinjector delivery, [Table 12](#). The mean and median time to active IM treatment delivery were 115 and 77 seconds respectively while the mean and median IV active treatment delivery were 415 and 325 seconds respectively. This examination reveals the IV active treatment delivery took 5 minutes longer than autoinjector delivery.

An examination of the time to treatment delivery by outcome success and treatment arm is performed. The mean and median time to treatment using IM autoinjector in the active treatment patient group with outcome success were 107 and 75 seconds respectively while the same metrics for the IV lorazepam successful outcome group were 391 and 304 seconds respectively. The mean difference between the successful outcome, active treatment, autoinjector and IV groups was 4.7 minutes. The mean and median time to treatment using the

¹⁰ RAMPART Clinical Study Report, Table 10, page 90

IM autoinjector in the active treatment patient group who had outcome failure (continued seizure at arrival to ED) were 137 and 90 seconds respectively while the same metrics for the IV lorazepam successful outcome group were 463 and 380 seconds respectively. The difference in mean time to active IM midazolam medication delivery in the successful outcome compared to outcome failure was 29.7 seconds while in the active IV lorazepam treatment group this difference was 71.3 seconds. The gap between active treatment, successful outcome IM midazolam treatment and outcome failure IV lorazepam has the largest difference in treatment latency of almost 6 minutes (5.92 minutes).

The same dataset examination is performed on the smaller ITT population, [Table 13](#) where results are similar.

Table 12 Time to Treatment Delivery by Autoinjector and Intravenous Route (including double dummy treatment access results), All Patients

			Time to Delivery by Autoinjector (IM) and IV (double dummy results)			
			Mean (seconds)		Median (seconds)	
Outcome (F=fail, S=Success)	Treatment Arm	Patients (includes Repeat enrollment)	IM	IV	IM	IV
All Patients						
		1023	110.6	407.2	77	324.5
All Patients by Treatment Arm						
	IM	514	114.6	396.9	77	320
	IV	509	106.5	415.4	77	325
All Patients by Outcome and Treatment Arm						
F	IM	134	136.8	439	90	349
F	IV	193	117	462.5	78	380
S	IM	380	107.1	375.6	75	290
S	IV	316	99.6	391.2	73	304
Shaded cells active treatment delivery, unshaded cells dummy treatment delivery						

Table 13 Time to Treatment Delivery by Autoinjector and Intravenous Route (including double dummy treatment access results), ITT Population

			Time to Delivery by Autoinjector (IM) and IV (double dummy results)			
			Mean (seconds)		Median (seconds)	
Outcome (F=fail, S=Success)	Treatment Arm	Patients (ITT)	IM	IV	IM	IV
All (ITT) Patients						

			Time to Delivery by Autoinjector (IM) and IV (double dummy results)			
			Mean (seconds)		Median (seconds)	
Outcome (F=fail, S=Success)	Treatment Arm	Patients (ITT)	IM	IV	IM	IV
		893	111.0	397.3	77.5	312.0
All (ITT) Patients by Treatment Arm						
	IM	448	114.6	386.8	77.0	305.0
	IV	445	107.4	405.6	78.0	318.0
All (ITT) Patients by Outcome and Treatment Arm						
F	IM	119	139.8	431.2	90.0	348.0
F	IV	163	122.0	442.2	80.0	375.0
S	IM	329	106.0	362.7	75.0	287.0
S	IV	282	98.2	387.9	75.5	304.5
	Shaded cells represent active treatment delivery, unshaded cells dummy treatment delivery					

Reviewer Comment: The mean time to treatment delivery for both dummy and active treatment was approximately 5 minutes longer for IV lorazepam treatment than IM midazolam treatment. This difference was similar for the study population including repeat enrollment and the ITT population. The time difference between successful and unsuccessful outcome in the ITT population for the IM midazolam treatment group was 29 second and in the IV midazolam group was 73 seconds. The difference in the IM midazolam treatment group is unlikely to contribute to outcome failure. The 1 minute and 10 second difference in the IV lorazepam group may contribute to less effective outcome by allowing the additional 70 seconds of status epilepticus. The mean difference in time to treatment for the successful IM midazolam and IV lorazepam treatment groups was 4.7 minutes. This difference reveals that successful treatment may be accomplished with the IV delivery.

Seizure Termination

Time to seizure termination for both autoinjector (IM) and IV are examined for the total patient group including repeat enrollment patients. This patient group provides the largest sample to represent the time to seizure termination. The mean and median time to seizure termination in the IM midazolam group were 384 and 289 seconds respectively while in the IV lorazepam treatment arm the mean and median results were 437 and 330 seconds respectively. The difference between IM midazolam group mean time to seizure termination and for IV lorazepam time to seizure termination is 53 seconds, [Table 14](#).

The mean and median time to seizure termination between outcome success cohorts of IM midazolam and IV lorazepam are examined. In those with a successful cessation of seizures at arrival to the emergency room in the IM midazolam cohort the mean and media time to

cessation were 347 and 270 seconds respectively while in the IV lorazepam cohort the times to cessation were 395 and 328 seconds respectively (including re-enrollment), see [Table 14](#). This examination reveals the difference in mean time to cessation was 47 seconds greater in the IV lorazepam group with a difference in the median of 58 seconds. The time to seizure cessation includes the time taken for delivery of medication, either by autoinjector or set up of functioning IV access. The time to seizure cessation includes these procedures and will be longer for the IV lorazepam cohort. The difference in the mean time to seizure cessation between IM and IV cohorts is less than the difference in mean time to treatment delivery. The difference in time to treatment delivery among ITT patients with a successful outcome (and timestamp is present) is greater in the lorazepam treatment arm where it takes 4.7 minutes longer for IV delivery, [Table 13](#).

If both IV lorazepam and IM midazolam required equivalent time for the therapeutic effect of seizure cessation then the difference, noted above, between the two means or medians of IM and IV cohorts should be near 5 minutes rather than only 47 seconds longer for the IV cohort. This difference is likely due to the more rapid systemic availability of the intravenous lorazepam once delivery is accomplished. The results computed from the smaller ITT population (repeat enrollment excluded) are similar to those from the larger cohort containing the repeat enrollment patients, with a time to seizure termination difference of 45 seconds between IM midazolam and IV lorazepam in patients with a successful treatment outcome, [Table 15](#).

Table 14 Time to Seizure Termination by Autoinjector and Intravenous Route (active treatment results), All Patients

Time to Seizure Termination by Outcome and Treatment Arm (total seconds)				
outcome, F= fail, S= success	Treatment arm	Patients (includes repeat enrollment)	Mean (total seconds)	Median (total seconds)
Time by Treatment Arm				
	IM	514	383.8	289
	IV	509	437.3	330
Time by Treatment Arm and Outcome				
F	IM	134	535.9	497.5
F	IV	193	519.8	347
S	IM	380	346.7	270
S	IV	316	395.3	327.5

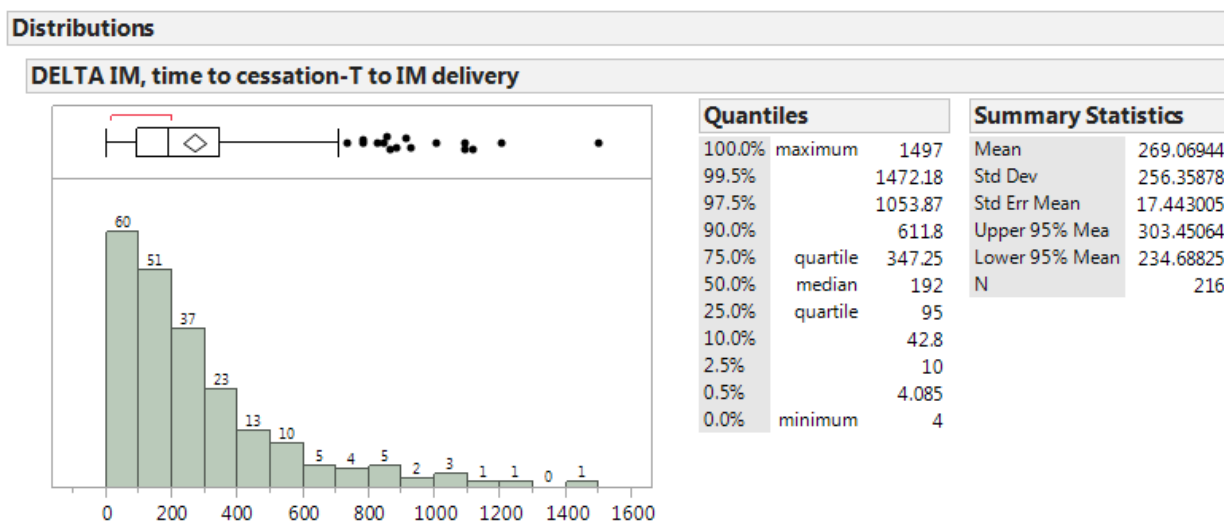
Table 15 Time to Seizure Termination by Autoinjector and Intravenous Route, ITT Population

Time to Seizure Termination by Outcome and Treatment Arm (total seconds)				
outcome, F= fail, S= success	Treatment arm	Patients (ITT)	Mean (total seconds)	Median (total seconds)
Time by Treatment Arm				
	IM	448	393.1	291
	IV	445	437.3	322
Time by Treatment Arm and Outcome				
F	IM	119	547.0	509
F	IV	163	518.0	312.5
S	IM	329	354.4	270.5
S	IV	282	398.5	322

IM midazolam, Latency from Administration to Seizure Cessation

The latency from administration of IM midazolam to cessation of seizures in the cohort with a successful outcome of seizure cessation at time of ED arrival is examined. There were 329 patients assigned to active IM midazolam treatment who had a positive outcome of cessation of seizures at the ED. Two hundred and sixteen (216) of these patients had a recording of time to seizure cessation and time to treatment delivery. This represents 66% of the available successful IM cohort with both time measurements. These patients allow a measurable latency for the time from medication administration to time of seizure cessation. The mean and median measure of this latency were 269 and 192 seconds respectively, [Figure 2](#).

Figure 2 Latency from Time of IM midazolam delivery to Seizure Cessation, Successful Outcome Cohort with Measures of Both Time to IM Administration and Time to Seizure Cessation



IV lorazepam, Latency from Administration to Seizure Cessation

The latency from administration of IV lorazepam to cessation of seizures in the cohort with a successful outcome of seizure cessation at time of ED arrival is examined. There were 282 patients assigned to active IM midazolam treatment who had a positive outcome of cessation of seizures at the ED. One hundred and thirty (129) of these patients had both a recording of time to seizure cessation and time to treatment delivery. This represents 46% of the available successful IM cohort with both time measurements. These patients allow computation of latency for the time from medication administration to time of seizure cessation. The mean and median measure of this latency were 89 and 78 seconds respectively, [Figure 3](#). There were 14 patients with a negative latency from seizure cessation to medication administration. The best explanation for a negative latency is that seizure cessation occurred before placement of an intravenous access while the clock is still running for IV placement or there is a recording error. This distribution of negative time results is shown in [Figure 4](#) for the reader. The values for these events ranged from -80 to – 1235 (20.6 minutes) seconds. A latency to seizure cessation computation following IV administration is performed with these patients excluded to obtain a more realistic measure. This yields a mean and median latency from medication administration of 165 and 96 seconds respectively, [Figure 5](#).

Figure 3 Latency from Time of IV lorazepam delivery to Seizure Cessation, Successful Outcome Cohort with Measures of Both Time to IM Administration and Time to Seizure Cessation

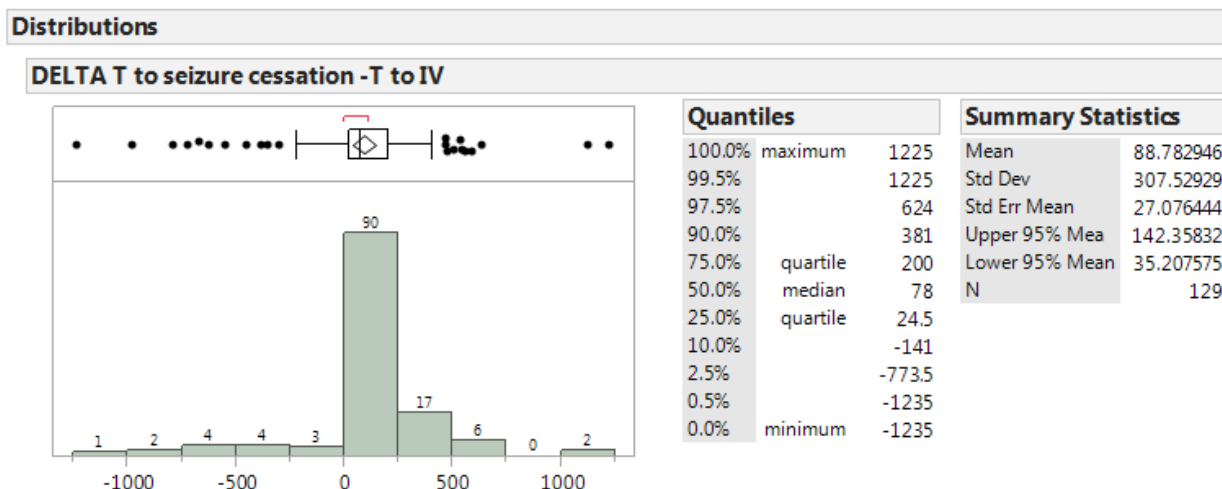


Figure 4 Patients with a Negative Latency from Time of IV lorazepam delivery to Seizure Cessation, Successful Outcome Cohort with Measures of Both Time to IM Administration and Time to Seizure Cessation

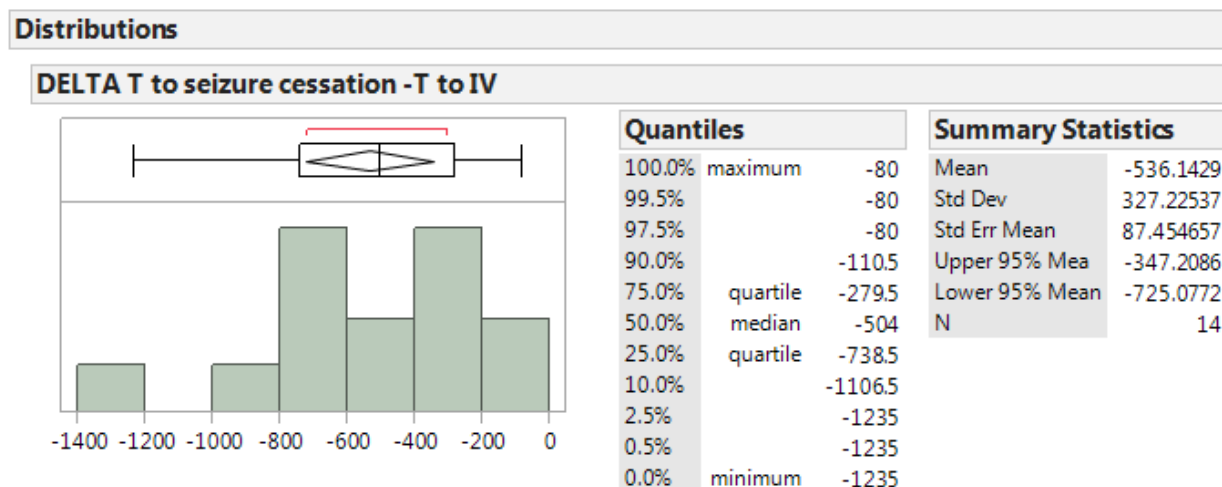
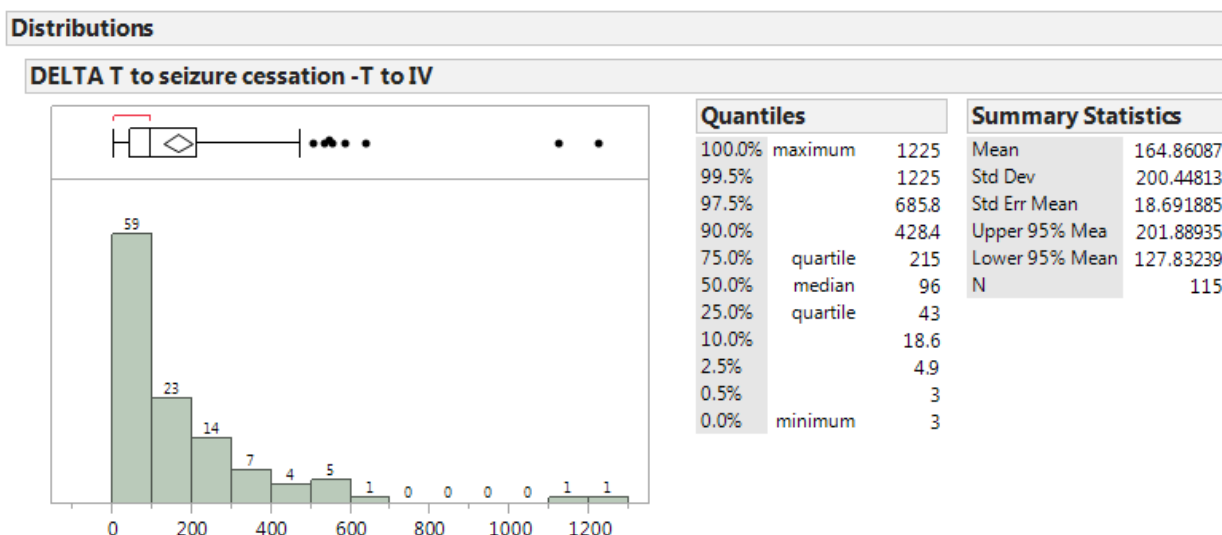


Figure 5 Latency from Time of IV lorazepam delivery to Seizure Cessation, Successful Outcome Cohort with Measures of Both Time to IM Administration and Time to Seizure Cessation, Patients with Negative Latency Excluded



Overall, the mean and median time from medication administration to seizure cessation for the IM midazolam treatment cohort are 269 and 192 seconds respectively. In the IV lorazepam cohort the mean and median time from medication administration to seizure cessation are 165 and 96 seconds respectively. The difference between the means and medians of the latency from medication administration to seizure cessation for IM midazolam compared to IV lorazepam are -1.7 and -1.6 minutes respectively where IM midazolam has a greater time to seizure cessation as discussed also in [paragraph two](#) of this section.

Reviewer Comment: Examination of the time to seizure cessation reveals that although there is a more rapid time to IM medication delivery (IM start) than IV medication delivery (IV start) of 4.7 minutes the difference between the successful treatment cohorts of these medication arms in time to seizure cessation was only 47 seconds in favor of IM midazolam due to the more rapid action of intravenous lorazepam.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Single efficacy study only

7.1.1. Primary Endpoints

single efficacy study only

7.1.2. Secondary and Other Endpoints

single efficacy study only

7.1.3. Subpopulations

single efficacy study only

7.1.4. Dose and Dose-Response

single efficacy study only

7.1.5. Onset, Duration, and Durability of Efficacy Effects

single efficacy study only

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

IM midazolam allows effective early phase status epilepticus treatment to be extended to the out of hospital EMS environment or other situations where IV access is not rapidly available.

7.2.2. Other Relevant Benefits

Stability at room temperature

- IM midazolam has certain advantages as a therapy for use in pre-hospital emergency settings involving status epilepticus. Compared with the classical benzodiazepines, the fused imidazole ring of midazolam confers improved stability and altered metabolism, making midazolam unique among the benzodiazepines. When the diazepine ring opens reversibly at pH <4, it forms a highly stable, water soluble, primary amine derivative. This physiochemical property allows it to be formulated and injected as an aqueous solution that can be stored in a non-refrigerated environment.¹¹

Rapid absorption following IM injection

- Above pH 4, and therefore at physiological pH (i.e., in the muscle and blood stream), the

¹¹ ISE page 13

ring closes, with a half-life of <2 minutes, becoming a lipophilic compound. The time in an aqueous state improves absorption when midazolam is administered through IM injection and the lipophilic state preserves rapid CNS penetration. Following IM injection, the peak serum levels of midazolam are reached within approximately 20-30 minutes (T_{max}).¹²

7.3. Integrated Assessment of Effectiveness

8. Review of Safety

8.1. Safety Review Approach

In the examination of serious adverse events and treatment emergent adverse events the entries in RAMPART ADAE dataset ITT population flag are utilized for analysis. Subsequently for these same sections (SAE, TEAE) the MRP, ADSE datasets for all patient enrollments are utilized for analysis. There are significant adverse events to address. These are events of respiratory compromise, a concern with a benzodiazepine central nervous system depressant. In addition, there are events of renal dysfunction. Rather than address these in section 8.4.4 “Significant Adverse Events” these are entered in section 8.5 “analysis of Submission Specific Safety Issues and given individual subheadings. The same strategy of addressing the RAMPART ITT population first, then followed by analysis of the MRP ADSE dataset for all patients is maintained.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Treatment in this study consisted of a single dose of study drug administered in the ambulance. Per the protocol, all subjects were to receive both an IM and an IV injection: IM midazolam followed by IV placebo, or IM placebo followed by IV lorazepam. Among the subjects in the ITT Population, 448 subjects were randomized to receive IM midazolam and 445 subjects were randomized to receive IV lorazepam. Of these 893 subjects, 85 subjects account for 130 re-enrollments into the study and received additional IM and IV injections for a total of 1023

¹² ISS page 14

subject enrollments and randomizations (514 IM midazolam and 509 IV lorazepam).

8.2.2. Relevant characteristics of the safety population:

The key underlying characteristic of the safety population is the situation of an extreme medical emergency at the time of study enrollment. Patients were enrolled directly from the community by 1st responders. These patients were in status epilepticus. A core characteristic is the profile of serious medical comorbidities that may be associated with status epilepticus, in addition to the potential for serious medical complications that may occur due to status epilepticus.

8.2.3. Adequacy of the safety database:

The RAMPART study ended at the arrival to the emergency department. Safety events in transit or ongoing at the time of emergency department were captured. Follow up safety data for patient that were not discharged from the hospital after treatment were not captured. To provide safety data on those patients where were admitted to the hospital and extract more complete safety data from all hospital records of RAMPART patients the Medical Records Project (MRP) was undertaken. Key information that was extracted from the medical records, analyzed, and presented in The MRP is intended to provide a more thorough understanding of the safety events, serious safety events, and safety events of interest (specifically, respiratory depression and renal failure) that were experienced by RAMPART clinical study participants.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

8.3.2. Categorization of Adverse Events

Treatment Emergent Adverse Events (TEAE)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that first occurred, or worsened in intensity, after initiation of midazolam treatment.

Serious Adverse Event

SAE was defined as an adverse event that was fatal or life threatening, was permanently or substantially disabling, required or prolonged hospitalization, resulted in a congenital anomaly,

required intervention to prevent permanent impairment or damage, or any event that the treating clinician or internal medical monitor judged to be a significant hazard, contraindication, side effect, or precaution.

8.3.3. Routine Clinical Tests

Routing clinical testing was not performed in this field trial in a medical emergency setting of status epilepticus

8.4. Safety Results

Deaths

In the overall RAMPART study (RAMPART and MRP) there were a total of 22 deaths: 13 in the IM midazolam treatment group and 9 in the IV lorazepam treatment group.

Examination of the RAMPART adverse (ADAE) dataset identifies 17 patients with a fatal outcome. Ten of these patients were in the IM midazolam treatment group while 7 were in the IV lorazepam group. This total fatal outcome agrees with the number presented in the RAMPART study ISS.

The preferred terms with >1 occurrence identified with a fatal outcome were “cardio-respiratory arrest” (3 patients), “Brain injury” (2 patients), “Cardiac arrest” (2 patients), “Metastases to central nervous system” (2 patients), “septic shock” (2 patients), status epilepticus (2 patients), see [Table 16](#).

Examination of the profile of adverse safety events that occurred in this patient subset reveals that 22 patients had 420 safety event instances. From among these the most frequent events were in more than 20% of the cohort with a fatal outcome were “respiratory failure” (46%), “acute kidney injury (41%)”, “hypertension” (41%), “status epilepticus” (41%) “hypokalemia” (36%), “pleural effusion” (36%), “pneumonia” (27%), “cardiac arrest” (23%), “hyperglycemia” (23%), “hypomagnesemia” (23%), “hypotension” (23%), “pneumonia aspiration” (23%), “pulmonary oedema” (23%), “seizure” (23%), “thrombocytopenia” (23%) and “urinary tract infection” (23%).

Table 16 Death Events, Preferred Terms, All RAMPART and MRP Reports

PREFERRED TERM	IM	IV
CARDIO-RESPIRATORY ARREST	2	1
CARDIAC ARREST	2	0
METASTASES TO CENTRAL NERVOUS SYSTEM	2	0
STATUS EPILEPTICUS	1	2

SEPTIC SHOCK	1	1	
BRAIN HERNIATION	1	0	
CEREBRAL HAEMORRHAGE	1	0	
CEREBRAL INFARCTION, CEREBROVASCULAR ACCIDENT	1	0	
PULSELESS ELECTRICAL ACTIVITY	1	0	
RESPIRATORY FAILURE	1	0	
BRAIN INJURY	0	2	
BRAIN DEATH	0	1	
BRAIN HYPOXIA	0	1	
ENTEROCOCCAL SEPSIS	0	1	Total
Total	13	9	22

A table of all fatal outcomes in the RAMPART trial with a brief narrative and assessment of cause of death is shown in [Table 17](#). There are 13 (59% of deaths) deaths in the IM midazolam treatment arm and 9 (41% of deaths) deaths in the IV lorazepam treatment arm. On review of the narrative reports, all deaths are due to a severe interceding medical complication of status epilepticus, severe worsening of an existing co-morbidity or emergence of a new catastrophic medical disorder (i.e. including cerebral hemorrhage), see [Table 17](#) "Death causality" column. In one case, patient 750, in the IM midazolam treatment arm the patient suffered a cardiac arrest after IM midazolam treatment. The duration of seizure is uncertain but the on arrival the patient was found to have an O₂ saturation of 64% with a pulse of 140 before the cardiac arrest. This history is consisted with a prolonged status epilepticus event.

Table 17 All Death (22), Brief Narrative Summary, Cause of Death (IM midazolam n=13, IV lorazepam n=9)

Patient ID	Treatment	Treatment arm	Narrative Summary	Death causality
(b) (6)	1	IM Midazolam	66 yo w female, Severe underlying co-morbidities, CNS metastasis, brain hemorrhage	Death due to brain hemorrhage
	1	IM Midazolam	68 yo B male, Prolonged episode of SE, administered study drug then cardiac arrest. Underlying medical status uncertain. Severe brain injury due to blunt force injury 13 years prior.	Uncertain. Likely complication of SE
	1	IM Midazolam	55 yo B male, Multiple hemorrhagic mass lesions from brain metastatic lesions. Cerebral edema with midline shift	Death due to multiple hemorrhage mass lesions from metastatic cancer
	1	IM Midazolam	59 yo w male, Possible amphetamine OD, patient posturing, severely hypertensive on ED arrival, Respiratory failure. Pt had cardiac arrest and died 4 days after	Death anoxic encephalopathy from initial SE episode,

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(b) (6)			admission. Death due to complications of initial SE event	
	1	IM Midazolam	60 B male, nursing home resident, Patient received low dose tier midazolam, treatment success at ED, recurrence of SE day 2 then refractory. Severe underlying medical compromise. Death 7 days after admission	Death due to recurrent SE after hospital admission, medical comorbidities
	1	IM Midazolam	21 yo B male hx of mental retardation, stroke age 4. Seizure stopped after IM treatment but cardiac arrest shortly thereafter with monitor showing asystole. Arrest continued with death	Possible temporal relationship
	1	IM Midazolam	64 yo W female with intracerebral bleed and impending herniation	Death due to IC bleed , herniation
	1	IM Midazolam	68 yo Asian female , underlying breast cancer, new multiple strokes, pt in coma after seizure treatment, died 8 days after admission	Death due to multiple strokes
	1	IM Midazolam	55 yo w female, seizure, fall, response to IM midazolam but found to have subdural and subarachnoid bleeding, hemorrhagic contusion. Subsequent mass effect and uncal herniation. Died 16 days after admission	Death due to seizure with head injury and severe intracerebral bleeding
	1	IM Midazolam	53 yo B female with large IV cerebral hemorrhage.	Death due to large intracerebral hemorrhage.
	1	10mg midazolam	59 yo B male, no seizure history. Parkinson's disease, ETOH abuse, CAD, Anemia, HTN, DM. no Seizure on ED arrival. CT brain unrevealing. Creatinine 1.2. Glucose 177. Coagulopathy due to underlying sepsis.. Chest X ray revealed retrocardiac atelectasis or infiltrates. Dx acute tubular necrosis on day 2 creatinine 1.7mg/dl. enterococcal bacteremia sepsis on day 4 after arrival. Day 7 after admission, pneumonia, disseminated intravascular coagulation. Death 64 days after admission	Death due to underlying medical compromise, development of sepsis, multiorgan failure. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	1	IM midazolam 10mg	67 yo w female, Medical history: partial tumor resection at the level of pons, hydrocephalus, multiple vasculo-peritoneal shunt	Patient had severe CKD at admission. Death due to unremitting seizures, underlying medical

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			placements. On arrival to ED seizures continue Subsequent multiple doses of lorazepam with resulting respiratory failure. Troponin was 3.77 and the subject was diagnosed with non-ST segment elevation myocardial infraction. CK 7679, BP 77/62, improved with fluid resuscitation. Pseudomonas pneumonia 9 days after admission. Unremitting seizure throughout the hospitalization. Death 29 days after admission	compromise. RF SMQ term is a secondary event and did not result directly from medication or treatment method
(b) (6)	1	Assigned Im midazolam 10mg (not delivered)	53 yo B male. Pertinent medical history: laryngeal carcinoma surgery, left hilar calcified granuloma, delirium tremens, alcohol abuse, congestive heart failure, hypertension, hypothyroidism. Upon arrival to ED seizure continued. Patient treated in transit only with rescue diazepam. After arrival treated with lorazepam and phenytoin. Also in respiratory failure and was intubated. CT head revealed large intraparenchymal bleed. No midline shift. Hypertension on admission, max reading 220mmHg systolic. Max diastolic 170mmhg. Creatinine on admission 2mg/dl. Underlying cerebral hemorrhage enlarged with midline shift. 7 days after admission the patient had a cardiopulmonary arrest.	Death due to underlying medical compromise with inability to sustain the stress of large intracerebral hemorrhage. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	0	IV Lorazepam	30 yo Alaskan native, with refractory SE, cerebral edema	Death refractory SE and complications
	0	IV Lorazepam	84 yo w female, respiratory compromise after admission. Primary lung cancer. DNR status on hospital admission	Death the day after admission due to respiratory compromise
	0	4mg lorazepam in narrative, high dose in ADCR dataset	60yo B female, Underlying CKD, CV disease, seizure onset after sleeping?, received assigned study drug lorazepam and midazolam. Treatment failure due to rescue med but not seizure in ER. Hypoxemia on arrival to ER pCO2 67, required PEEP, BP 254/136 with subsequent	RF SMQ due to underlying severe multiorgan compromise. 2nd event.

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			drop to 88/55. Non-ST elevation MI Tropoinin 1.89. 4 days post admission multiple cerebral infarcts with hemorrhagic component. Positive sub-falcine shift. Death 4 days post admission.	
(b) (6)	0	IV lorazepam low dose	74 yo Female, history of renal transplant, stage 2 colon cancer. Severe peripheral vascular disease. No seizure on arrival to ER. Complex medical course after admission, death from septic shock (persistent enterococcal bacteremia), death 58 days after admission	Death due to underlying medical compromise, development of sepsis, multiorgan failure. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	0	IV lorazepam 4mg.	62 yo B female, no seizure history. Medical history: pertinent medical history of pituitary macroadenoma with transsphenoidal hypophysectomy, gamma knife stereotactic radiosurgery, panhypopituitarism, hydrocephalus, ventriculo-peritoneal shunt placement, depression, encephalopathy, shock, respiratory distress, unspecified chest pain, nephrolithiasis with lithotripsy, chronic kidney disease, recurrent urinary tract infections, hypertension, anemia, thrombocytopenia, pancytopenia, chronic pancreatitis, diabetes mellitus, diabetes insipidus, hypoglycemia, hyponatremia, chronic pain syndrome, hypothermia, gait instability, septicemia, abscess and cellulitis of the foot, hepatitis C, alcohol abuse, and obesity. On arrival to ED no seizures Intubated due to respiratory failure. SE resumed. CT revealed large intracerebral bleed. BP 53/32. Dx septic shock. Patient had fluid and pressor resuscitation with BP improvement to 101/57. Death occurred 7 days after admission when life support withdrawn	Death due to large intracerebral hemorrhage and cerebral hypoxia. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	0	IV lorazepam 4mg	53 yo B female, Medical history of multiple strokes, dementia, CHF,	Death due to continued status epilepticus and underlying medical compromise leaving

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			COPD, DM type 2, HTN cocaine abuse. Upon ED arrival SE was ongoing. Respiratory failure and respiratory acidosis. BP 82/58. Creatinine 1.88 . Day 2 patient had EEC consistent with partial SE of left hemisphere. Pt in burst suppression EEG 2 days after admission. On day 4 found to have pancytopenia, hb 7.7 g/dl continued to drop from admission and pt received second of two blood transfusions (4 units total).	patient unable to tolerate the stress of sustained SE and resulting treatment. RF SMQ term is a secondary event and did not result directly from medication or treatment method
(b) (6)	0	IV lorazepam 4mg	78 yo B male. Pertinent medical history of infarct in the right frontal parietal lobe, tardive dyskinesia, dementia, paranoid schizophrenia, post-traumatic stress disorder, congestive heart failure, chronic venous stasis, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, and obesity. Upon arrival to ED seizure continued but successfully treated with lorazepam and phenytoin. Glucose 285mg/dl. On day 2 of hospital admission the patient developed fever and hypoxia (po2 59mmHg) with hypotension, BP 75/48. Subsequent CXR consistent with aspiration pneumonia. Creatinine 1.5mg/dl, BUN 21 mg/dl. 8 days after admission acute kidney injury considered resolved (creatinine 1.3mg/dl). Patient subsequently had worsening pulmonary status due to pneumonia. The patient died 21 days after admission due to cardio pulmonary arrest.	Death due to underlying medical compromise, development of persistent and worsening pneumonia and cardiopulmonary arrest. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	0	IV lorazepam	19 yo B male , no pertinent medical history. Prior to EMS arrival the patient had suicidal ideation, ingested quetiapine. Agonal breathing and grand mal seizure activity are reported. Patient had 4mg IV lorazepam and rescue diazepam prior to ED arrival. Patient not having seizures on ED arrival. After arrival patient had grand mal seizure activity successfully treated but is reported to be pulseless and apneic, then placed on ventilatory. Text	Death due to severe SE, hypoxic encephalopathy and cerebral herniation. RF SMQ term is a secondary event and did not result directly from medication or treatment method

			consistent with advance cardiac life support procedures. Severe hypoxic encephalopathy reported. Post arrest creatinine 2mg/dl with BUN 17mg/dl. The subject's serum drug screen was positive for tricyclic antidepressants and his seizures and arrest were deemed to be induced by a poisoning of tricyclic antidepressants. Glucose 302mg/dl. 4 days after admission CT scan of head revealed a marked increase in intracranial edema. Herniation seen at the foramen magnum and loss of white matter distinction. Brain death protocol initiated and patient subsequently declared brain dead.	
(b) (6)		0 IV Lorazepam 4mg	84 yo Asian female, pertinent MH: subdural hemorrhage, dementia, hypertension, rectal cancer, pneumonia. cachexia, malnutrition, chronic hypokalemia, chronic anemia, possible peritonitis. Upon ED arrival no seizures. Seizure later recurred with lorazepam treatment and respiratory failure. Blood cultures revealed enterococcal septicemia. CXR revealed CHF, left pleural effusion with possible pneumonia. BP 90/55 with hypokalemia, hypomagnesemia, anemia (day 2) hb 6.8g/dl. effusion. Twenty-four hours post admission, she was only flexing to pain with no verbalization. 1st day post admission creatinine 0.8mg/dl with BUN 3mg/dl. Life support withdrawn with death on day 4 post admission.	Death due to underlying medical compromise, development of sepsis, multiorgan failure. RF SMQ term is a secondary event and did not result directly from medication or treatment method

Reviewer Comment: There is an excess of deaths in the IM midazolam treatment arm over the IV lorazepam treatment arm by a margin of 59% to 41% while the death rate among all enrollments in the IM midazolam is 2.5% and in the IV lorazepam treatment arm is 1.8%. The frequency of fatal outcome in the circumstance of the severe physiologic challenge of status epilepticus is approximately 20%.¹³ In a retrospective study of 74 patients admitted to

¹³ Lowenstein DH, Alldredge BK. Status Epilepticus. New England Journal of Medicine 1998;338:970-976. DOI: 10.1056/NEJM199804023381407

Columbia–Presbyterian Medical Center with status epilepticus 21% of episodes were fatal while a retrospective study of 49 cases with convulsive status epilepticus and cardiac arrest the first reported rhythm in 51% of these patients was asystole.^{14, 15} The single death with cardiac arrest in patient ID (b) (6), not explained by co-morbidity, new catastrophic medical disease or a clearly recorded refractory status epileptics may be the result of a prolonged event before EMS arrival where the 1st O₂ saturation measurement was 64%. The identification of asystole on cardiac monitoring is also in alignment with the features of cardiac arrest in severe convulsive status epilepticus. The overall death rate in the IM midazolam of 2.5% is low in comparison to the reported fatal outcome of SE in the medical literature, noted above, and does not indicate a safety signal for IM midazolam treatment.

8.4.2. Serious Adverse Events

RAMPART

The frequency of SAEs was lower in the IM midazolam group. In the ITT Population, 271 (30.3%) subjects had an SAE: 126 (28.1%) subjects in the IM midazolam group and 145 (32.6%) subjects in the IV lorazepam group.

The SAEs with a frequency > 1% are examined in the IM midazolam and IV lorazepam arm are examined. There were six SAE preferred terms with a frequency ≥2% in either the IM midazolam or IV lorazepam group. The most frequent serious adverse events in the IM midazolam treatment arm ≥2% were “convulsion (6.5%), “upper airway obstruction” (4.9%), “respiratory depression” (3.6%), “mental status change” (2.5%), and “coma” (2%). The frequency of “convulsion”, “respiratory depression”, and “coma” were lower in the IM midazolam than in the IV lorazepam treatment arm while “upper airway obstruction”, and “mental status change” were lower in the IV lorazepam treatment arm, see [Table 18](#).

Table 18 RAMPART Serious Adverse Events ≥ 1% of patients by Treatment Arm, ITT.

	# patients	% IM midazolam arm	# patients	% IV lorazepam arm
Convulsion	29	6.5	35	7.9
Upper airway obstruction	22	4.9	12	2.7
Respiratory depression	16	3.6	23	5.2
Mental status changes	11	2.5	8	1.8
Coma	9	2	11	2.5
Unresponsive to stimuli	8	1.8	11	2.5

¹⁴ J. Claassen, J. K. Lokin, B.-F. M. Fitzsimmons, F. A. Mendelsohn, S. A. Mayer. Predictors of functional disability and mortality after status epilepticus. *Neurology* Jan 2002, 58 (1) 139-142; DOI: 10.1212/WNL.58.1.139

¹⁵ Legriel, S, et. al. Cardiac Arrest in Patients Managed for Convulsive Status Epilepticus: Characteristics, Predictors, and Outcome. *Critical Care Medicine*. August 2018 • Volume 46 • Number 8.
DOI:10.1097/CCM.0000000000003196

Postictal state	7	1.6	8	1.8
Respiratory failure	7	1.6	16	3.6
Sepsis	6	1.3	6	1.3
Hypotension	5	1.1	6	1.3
Renal failure acute	5	1.1	0	0
Rhabdomyolysis	5	1.1	5	1.1
Pneumonia aspiration	0	0	5	1.1
Alcohol withdrawal syndrome	0	0	5	1.1

A single adverse event in a healthy subject in study 1005 prompts an examination for the term “thrombocytopenia” in the RAMPART and MRP datasets. There was a single adverse event of preferred term “thrombocytopenia” in the IV lorazepam arm of the RAMPART study. This event is also captured in the MRP dataset. Discussion that includes the non-serious “thrombocytopenia” entries is presented in the RAMPART [TEAE presentation](#).

MRP

Events that are characterized in the Medical Records Project (MRP) adverse safety events as Serious adverse events are examined. There were 14 preferred terms with entries as SAEs in $\geq 2\%$ of patients in either treatment arm. The frequency of these events was greater in the IV lorazepam than in the IM midazolam treatment arm in 11 of these 14 preferred terms. Terms with frequency greater than 5% in either treatment arm include “seizure”, “status epilepticus”, “respiratory failure”, “post ictal state”, “acute kidney injury” and “acute respiratory failure”. The frequency of all but “acute kidney injury” were greater in the IV lorazepam treatment arm. The frequency of “acute kidney injury” was 5.8% in the IM midazolam treatment group and 3.8% in the IV lorazepam group, see

Table 19 MRP All Patients, Serious Adverse events (SAE) from Safety Events Dataset by Treatment arm (ADSE dataset)

	IM midazolam n= 514 (includes repeat enrollment)		IV lorazepam n= 509 (includes repeat enrollment)	
Preferred Term	# patients	% IM Patients	# patients	% IV Patients
SEIZURE	71	13.8	71	13.9
STATUS EPILEPTICUS	57	11.1	80	15.7
RESPIRATORY FAILURE	48	9.3	66	13.0
POSTICTAL STATE	38	7.4	48	9.4
ACUTE KIDNEY INJURY	28	5.4	17	3.3
ACUTE RESPIRATORY FAILURE	26	5.1	35	6.9
GENERALISED TONIC-CLONIC SEIZURE	11	2.1	12	2.4
MENTAL STATUS CHANGES	10	1.9	10	2.0
RHABDOMYOLYSIS	10	1.9	6	1.2

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Seizalam (midazolam IM injection)

HYPOTENSION	9	1.8	6	1.2
PNEUMONIA ASPIRATION	9	1.8	12	2.4
PNEUMONIA	8	1.6	14	2.8
RESPIRATORY DISTRESS	7	1.4	9	1.8
SEPSIS	7	1.4	9	1.8

Reviewer Comment: The most frequency serious adverse events are consistent with the severity of the underlying illness. These events include epilepsy related terms “convulsion”, “seizure”, and “status epilepticus”. The frequency of all three are higher in the IV lorazepam treatment arm. There is also a high frequency of terms related to respiratory compromise. These terms include “upper airway obstruction”, “respiratory depression”, “respiratory failure”, “acute respiratory failure” and “respiratory distress”. The frequency for all of these terms except “upper airway obstruction” is greater in the IV lorazepam treatment arm. The adverse reaction frequency for epilepsy and respiratory related SAEs is lower in the IM midazolam treatment arm.

Study 1005

There was a single serious adverse event in study 1005. This subject had an adverse event preferred term of “thrombocytopenia”. This patient was later found to have a diagnosis of thrombocytopenia due to idiopathic thrombocytopenic purpura, narrative below.

Subject (b) (6) Thrombocytopenia

Subject (b) (6) is a 23 yo female on Depo-Provera. The subject had a baseline (Screening) platelet count was 155 thou/ μ L; however, the Investigator considered this value not clinically significant and approved the subject for enrollment. On Day 15, the count dropped to 59 thou/ μ L and on Day 27, the count decreased to 20 thou/ μ L. On Day 28, Subject (b) (6) was contacted and advised to go to the emergency room for evaluation. The subject was admitted to a local medical center on Day 28 and administered oral methylprednisolone 60 mg bid and ferrous sulfate 325 mg tid. She was discharged 3 days later (Day 31) with a diagnosis of: 1) thrombocytopenia due to idiopathic thrombocytopenic purpura; and 2) iron-deficient anemia. Her platelet count on the day of discharge was 53 thou/ μ L.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

This study consisted of a single treatment during a crisis event. The patient, due to the nature of status epilepticus, is not conscious during status epilepticus. Status epilepticus may be a life-threatening event. Due to these circumstances, there is no opportunity to withdraw or drop out of the study. The duration of the RAMPART study is the time from EMS contact until arrival at the RAMPART participating emergency department.

8.4.4. Significant Adverse Events

Significant Adverse Events in the RAMPART study and MRP were events of respiratory compromise, renal dysfunction and rhabdomyolysis. These are discussed fully [in Section 8.5 Analysis of Submission-Specific Safety Issues](#).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

RAMPART

Due to the short, single treatment event, of the study the profile of and frequency of adverse events is smaller than a study with a longer treatment interval of several weeks. There were 977 adverse event entries from all 1023 study enrollments. There is a single adverse entry for 967 patients and 5 patients have two adverse event term entries. For the total enrollment population, there were 188 preferred term entries where there were 23 terms with 10 or more instances of entry. The most frequent 5 preferred term entries were “convulsion”, “respiratory depression”, “agitation”, “upper airway obstruction” and “pyrexia”

The RAMPART ADAE dataset is examined to compare frequency of preferred terms between the IM midazolam and IV lorazepam treatment arms in the ITT population. Adverse events with a frequency greater than 1% in the IM midazolam treatment are compared to the corresponding term in the IV lorazepam treatment arm, see [Table 20](#). There were 20 terms captured with a frequency >1% in the IM midazolam treatment arm. The most frequent adverse event preferred term is “convulsion”. The frequency of convulsion in the IM midazolam and IV lorazepam treatment arm was 13.8% and 14.6% respectively. Events with a higher frequency in the IM midazolam treatment arm were “Upper airway obstruction”, “Agitation”, “Pyrexia”, “Mental status changes”, “Postictal state”, “Renal failure acute”, “Metabolic acidosis”, “Hypomagnesaemia”, “Leukocytosis”. The terms “upper airway obstruction”, “renal failure acute” and “hypomagnesaemia” had the most notable increase in frequency in the IM midazolam over IV lorazepam treatment arm at multiples of 1.8, 1.8, and 2.8 respectively.

Table 20 RAMPART, TEAE with >1% Frequency in IM midazolam Compared to the Corresponding Term in IV lorazepam treatment arm, ITT Population

Preferred Term	IM midazolam (n= 448)		IV lorazepam (n= 445)		Group Comparisons	
	IM # Patients	IM % Patients	IM # Patients	% IV Patients	delta IV-IM	multiple of IM
Convulsion	62	13.8	65	14.6	0.8	0.9
Upper airway obstruction	22	4.9	12	2.7	-2.2	1.8
Respiratory depression	19	4.2	29	6.5	2.3	0.6

Preferred Term	IM midazolam (n= 448)		IV lorazepam (n= 445)		Group Comparisons	
	IM # Patients	IM % Patients	IM # Patients	% IV Patients	delta IV-IM	multiple of IM
Agitation	16	3.6	13	2.9	-0.7	1.2
Pyrexia	16	3.6	15	3.4	-0.2	1.1
Hypotension	12	2.7	18	4	1.3	0.7
Mental status changes	12	2.7	10	2.2	-0.5	1.2
Postictal state	11	2.5	8	1.8	-0.7	1.4
Vomiting	10	2.2	17	3.8	1.6	0.6
Coma	9	2	11	2.5	0.5	0.8
Hypokalaemia	9	2	13	2.9	0.9	0.7
Renal failure acute	9	2	5	1.1	-0.9	1.8
Headache	8	1.8	11	2.5	0.7	0.7
Rhabdomyolysis	8	1.8	8	1.8	0	1.0
Unresponsive to stimuli	8	1.8	11	2.5	0.7	0.7
Respiratory failure	7	1.6	16	3.6	2	0.4
Metabolic acidosis	6	1.3	4	0.9	-0.4	1.4
Sepsis	6	1.3	7	1.6	0.3	0.8
Hypomagnesaemia	5	1.1	2	0.4	-0.7	2.8
Leukocytosis	5	1.1	4	0.9	-0.2	1.2

Reviewer Comment: The basis for the difference between groups in the terms where IM midazolam frequency exceeds IV lorazepam frequency is unclear. The term upper airway obstruction may be associated with aspiration of gastric contents during a seizure but this would also be expected to be seen as an increase in “pneumonia aspiration”, however the term “pneumonia aspiration” occurs with a frequency of 0.9% in the IM midazolam group (not shown) and is more frequent in the IV lorazepam group at 2.7% (not shown). This could also be due to a complication of head and neck position during seizure but it is not clear why this type of clinical feature would differ between treatment arms. It may be due only to differences in investigator observation and coding. The same conclusion is drawn concerning the other terms greater in IM midazolam and a similar reasoning may be applicable to the terms that have a higher frequency in the IV lorazepam population. The preferred term of interest, “renal failure acute” is discussed more fully in [section 8.5.4 Renal Dysfunction](#) where the final conclusion is similar. The higher frequency in the IM midazolam group for this term may be due to inequality in existing co-morbidities or severity of individual SE episodes.

MRP

All patient enrollments in the MRP, ADSE safety datasets are examined for frequency of events greater than 3%. There were 41 event terms with a frequency > 3%. From among these safety event terms there were 13 in the IM midazolam group with a frequency greater than the IV lorazepam treatment arm, the remaining 28 terms had a greater frequency in the IV lorazepam arm.

Among the 14 event terms with a frequency of greater than 5% there were 4 terms where the frequency was greater in the IM midazolam arm than in the IV lorazepam arm. These terms were “headache”, “hypotension”, “hypertension”, and “anemia”. The remaining terms were more frequent in the IV lorazepam arm, see [Table 21](#).

Table 21 MRP, All Patient Enrollments. Safety Events >3% in the IM midazolam Compared to Corresponding Event Terms in the IV lorazepam arm. (ADSE dataset)

	IM midazolam N= 514		IV lorazepam N= 509	
Preferred term	# IM	% IM	# IV	% IV
POSTICTAL STATE	80	15.6	95	18.7
SEIZURE	72	14	73	14.3
HEADACHE	60	11.7	49	9.6
STATUS EPILEPTICUS	57	11.1	80	15.7
RESPIRATORY FAILURE	49	9.5	67	13.2
HYPOKALAEMIA	46	8.9	48	9.4
HYPOTENSION	44	8.6	26	5.1
ACUTE KIDNEY INJURY	40	7.8	40	7.9
HYPERTENSION	35	6.8	31	6.1
CHEST X-RAY ABNORMAL	34	6.6	44	8.6
ATELECTASIS	28	5.4	32	6.3
ACUTE RESPIRATORY FAILURE	27	5.3	35	6.9
ANAEMIA	27	5.3	25	4.9
PYREXIA	27	5.3	29	5.7
URINARY TRACT INFECTION	24	4.7	27	5.3
VOMITING	24	4.7	28	5.5
NAUSEA	23	4.5	20	3.9
OEDEMA PERIPHERAL	22	4.3	29	5.7
CHEST PAIN	20	3.9	21	4.1
DIARRHOEA	20	3.9	21	4.1
HYPERGLYCAEMIA	20	3.9	32	6.3
HYPOMAGNESAEMIA	20	3.9	27	5.3
PAIN	20	3.9	22	4.3
PNEUMONIA	19	3.7	23	4.5
VENTRICULAR EXTRASYSTOLES	19	3.7	7	1.4
CARDIOMEGALY	18	3.5	10	2
RHABDOMYOLYSIS	18	3.5	11	2.2
RHONCHI	18	3.5	19	3.7
PLEURAL EFFUSION	17	3.3	19	3.7
PSYCHOGENIC SEIZURE	17	3.3	9	1.8
PULMONARY OEDEMA	17	3.3	11	2.2
DYSпноEA	16	3.1	14	2.8
PNEUMONIA ASPIRATION	16	3.1	25	4.9
SKIN ABRASION	16	3.1	13	2.6
THROMBOCYTOPENIA	16	3.1	19	3.7

TACHYCARDIA	10	1.9	18	3.5
ATRIAL FIBRILLATION	8	1.6	10	2
CARDIAC ARREST	5	1	2	0.4
ATRIAL FLUTTER	4	0.8	0	0
PULSELESS ELECTRICAL ACTIVITY	1	0.2	0	0
TORSADE DE POINTES	1	0.2	0	0

From the TEAE safety event term analysis there were 9 terms of increased interest identified. These terms were “seizure”, “status epilepticus”, “respiratory failure”, “acute kidney injury”, “acute respiratory failure”, “pneumonia”, “rhabdomyolysis”, “thrombocytopenia”, and “torsade de pointes”. These terms are of interest due to potential relationship to efficacy for example the seizure related terms and the remaining terms due to potential significant safety events related to IM midazolam treatment, see [Table 22](#). Examination of these results reveals two terms of special interest with a higher frequency in the IM midazolam arm than in the IV lorazepam arm. These events are “rhabdomyolysis” where the frequency in the IM midazolam arm is 1.6 x higher than the IV lorazepam and “torsade de pointes”. The case of “torsade de pointes” in patient (b) (6) is adjudicated later in the review discussion but is found to be due to underlying cardiac disease exacerbated by the severe medical stress of SE and hypoglycemia. The remaining event terms that are associated with severe medical complications of SE, including “acute kidney injury” are more frequent in the IV lorazepam treatment arm.

Table 22 MRP, All Patient Enrollments. Safety Events of Interest, IM midazolam Compared to Corresponding Event Terms in the IV lorazepam arm. (ADSE dataset)

Preferred Term	IM midazolam		IV lorazepam	
	# IM	% IM	# IV	% IV
SEIZURE	72	14	73	14.3
STATUS EPILEPTICUS	57	11.1	80	15.7
RESPIRATORY FAILURE	49	9.5	67	13.2
ACUTE KIDNEY INJURY	40	7.8	40	7.9
ACUTE RESPIRATORY FAILURE	27	5.3	35	6.9
PNEUMONIA	19	3.7	23	4.5
RHABDOMYOLYSIS	18	3.5	11	2.2
THROMBOCYTOPENIA	16	3.1	19	3.7
TORSADE DE POINTES	1	0.2	0	0

The adverse event preferred term “thrombocytopenia” is examined separately after a single healthy volunteer in study 1005 was found to have a serious adverse event of thrombocytopenia. Examination of the MRP ADSE dataset. Examination of this dataset will capture any occurrence of “thrombocytopenia” from RAMPART adverse event dataset or the MRP medical chart data extraction from the 1023 patient enrollments. This examination

identified 35 patients with a “thrombocytopenia” preferred term entry. These events had a frequency of 3.1% in the IM midazolam treatment arm and 3.7% of the IV lorazepam treatment arm. One event in the IV lorazepam arm was entered as an SAE. This patient had concurrent sepsis and systemic inflammatory response syndrome. The unequal distribution of these events with a greater proportion in the IV lorazepam treatment and the single SAE occurrence in the IV lorazepam arm does not support causal relationship, or a notable signal for thrombocytopenia due to IM midazolam.

Reviewer Comment: The adverse events in the RAMPART IM midazolam treatment arm with a notable increase in frequency over the IV lorazepam treatment arm are “upper airway obstruction” and “acute renal failure”. The basis for an excess of the respiratory term “upper airway obstruction” with the use of IM midazolam is unclear. It may be considered that this finding may be related to aspiration of gastric contents that could occur during status epilepticus, however, the frequency of “pneumonia aspiration” is three times greater in the IV lorazepam treatment arm. In the discussion of [respiratory compromise events](#) in Section 8.5 there is no overall difference in these events between treatment arms. The higher frequency of “renal failure acute” is also discussed in Section 8.5, [renal dysfunction](#).

Examination of these results reveals two terms of special interest with a higher frequency in the IM midazolam arm than in the IV lorazepam arm. These events are “rhabdomyolysis” where the frequency in the IM midazolam arm is 1.6 x higher than the IV lorazepam and “torsade de pointes” discussed later in the review.

The conclusion on events of renal dysfunction is these events are secondary to the severity of the status epilepticus episodes and distribution of the demographics of serious co-morbidities but unrelated to treatment arm.

Study 1005

Treatment emergent adverse events (TEAE) are examined in study 1005. Two events are predominant. These are the preferred terms “somnolence” and “injection site pain” with frequencies of 99.6 and 90.4 percent of subjects. Remaining preferred terms in the adverse event dataset have notably lower frequencies of occurrence. Following “injection site pain” the next most frequent adverse event is “headache” occurring in 9.2% of subjects. The term “oxygen saturation decreased” follows with a frequency of 5.2%. The remaining preferred terms with a frequency $\geq 1.6\%$ are “hiccups”, “cough”, “dizziness”, “nausea”, “back pain” and “vomiting”, see [Table 23](#).

Table 23 Study 1005, TEAE > 1.6%

PREFERRED TERM	# subjects	% Subjects
Somnolence	249	99.6

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Seizalam (midazolam IM injection)

Injection site pain	226	90.4
Headache	23	9.2
Oxygen saturation decreased	13	5.2
Hiccups	9	3.6
Cough	7	2.8
Dizziness	7	2.8
Nausea	6	2.4
Back pain	4	1.6
Vomiting	4	1.6

Reviewer Comment: the predominant adverse events, “somnolence” and “injection site pain” are not unexpected in these healthy subjects receiving a benzodiazepine treatment via two autoinjector administrations. Respiratory / ventilatory compromise are a concern in midazolam treatment and are reflected in the frequency of “oxygen saturation decreased”. The issue of respiratory compromise is discussed more fully in [section 8.5.5 Decreased Oxygen Saturation](#). Of note is the absence of preferred terms associated with renal failure or renal dysfunction unlike the SE patient population

8.4.6. Laboratory Findings

Laboratory studies were not captured in the RAMPART study.

Study 1005

In study 1005 Clinical Chemistry and Hematology Parameters were captured.

Mean Values

Laboratory mean parameters (serum chemistry and hematology) remained within reference range for all subjects at the Follow-Up assessment.

Shifts

Parameters are discussed if the direction of the shift possibly indicated safety concerns.

There was a shift in total protein from normal at Screening to low at the Follow-Up assessment for 26 (10%) subjects, including 17 (13%) males and 9 (8%) females. The lowest abnormal value did not go below 5.5 g/dL (reference range 6.3 - 8.7 g/dL).

Outliers

There were two laboratory AEs in this study. Subject (b) (6) exhibited the moderate SAE of

thrombocytopenia that required hospitalization. This SAE is discussed in Section 8.4.2

Subject (b) (6) (a 26-year-old female) exhibited the mild AE of increased blood triglycerides on Day 8, with a value of 489 mg/dL (reference range 37 - 288 mg/dL). Upon recheck 14 days later, the value returned to acceptable limits (310 mg/dL). It should be noted that this subject exhibited a triglyceride value of 311 mg/dL at Screening.

The reviewer examines serum creatinine values in the dc-aa dataset for high value flags. There were two subjects, (b) (6) with normal creatinine values at screening and out of reference range high post dose. Both subjects were found to have a post dose value of 1.26 mg/dl where high normal reference range is 1.22 mg/dl. The vital sign dataset for these subject is examined to determine if there was evidence of hemodynamic instability post dose and none is identified. The adverse event dataset daepaa.xpt is examined to determine if there were corresponding cardiac, pulmonary or renal adverse effects. None are identified. Both subjects had somnolence as an adverse effect.

8.4.7. Vital Signs

A vital sign dataset was not captured in the RAMPART study or MRP

Study 1005

In study 1005 the sponsor performed vital sign recordings at multiple pre-dose and post dose timepoints. Vital signs were taken while subjects were in the supine position.

Means

Mean blood pressure, respiratory rate, and pulse oximetry parameters were within normal limits at assessed post dose time points, with no marked mean changes from pre- dose. Generally, within the first hour post dose, there were slight mean decreases for both systolic (≤ 12 mm Hg overall) and diastolic (< 7 mm Hg overall) BPs. Mean pulse rates increased within the first hour post dose, with increases ranging from 8.5 to 10.5 bpm above mean baseline (64.8 bpm overall).

At the time of the pre- dose assessment, the mean respiratory rate was 16.0 ± 3.67 breaths/minute. Over time following dosing, mean respiratory rates were quite stable, with mean values remaining between 14.6 and 17.7 breaths/minute, and mean changes from baseline being no greater than 1.7 breaths/minute at any time point, with no apparent differences by gender.

At the pre- dose assessment, the mean oxygen saturation value was 98.8%. At 30 minutes

following dosing, the mean oxygen saturation dropped 3.4 percentage points to 95.5%. The oxygen saturation values did show some individual variability, with standard deviations between 1.32 and 2.90 percentage points, and it was not unusual for individual subjects to have values in the low 90s. The drop in mean saturation to 95.5% with a number of individual values in the low 90s is consistent with reported oxygen saturation values during sleep in normal individuals.¹⁶

Outliers

There was one subject with two vital sign AEs (moderate hypotension and moderate tachycardia). Subject (b) (6) (27-year-old female) exhibited a supine blood pressure of 59/37 mm Hg and pulse of 128 bpm at Hour 0.3. This subject also experienced two vomiting episodes immediately before these AEs. At Hour 0.5, the AEs were resolved, with a (supine) pressure of 112/74 mm Hg and pulse of 97 bpm. The Investigator considered both AEs to be probably related to study treatment.

8.4.8. Electrocardiograms (ECGs)

An ECG dataset was not captured in the RAMPART study or MRP

8.4.9. QT

QT interval is examined in Study 1005

ECG were captured only in the healthy volunteer studies. Study 1005 will be examined. This was study to evaluate the safety of IM administration of midazolam in 250 patients at of two 10mg IM midazolam autoinjector doses separated by <1 minute. T_{max} approximately .74 Hrs.

12-Lead ECG was performed at the following time points: three times within 20 minutes prior to Time 0 (defined as the time of the first midazolam injection) and then once within 5 minutes of each of the following time points: 10, 20, 30, and 60 minutes and 1.5, 3, 6, 12, 24, and 48 hours.

The sponsor dataset includes variables for QRS, PR QT, QTcB, Heart Rate, time of recording and a medical comment. The reviewer computes QTcF for each entry from heart rate and recorded QT interval as $QTcF = QT / \sqrt[3]{60/HR}$. The -0.28-hour entry is chosen as baseline. The baseline

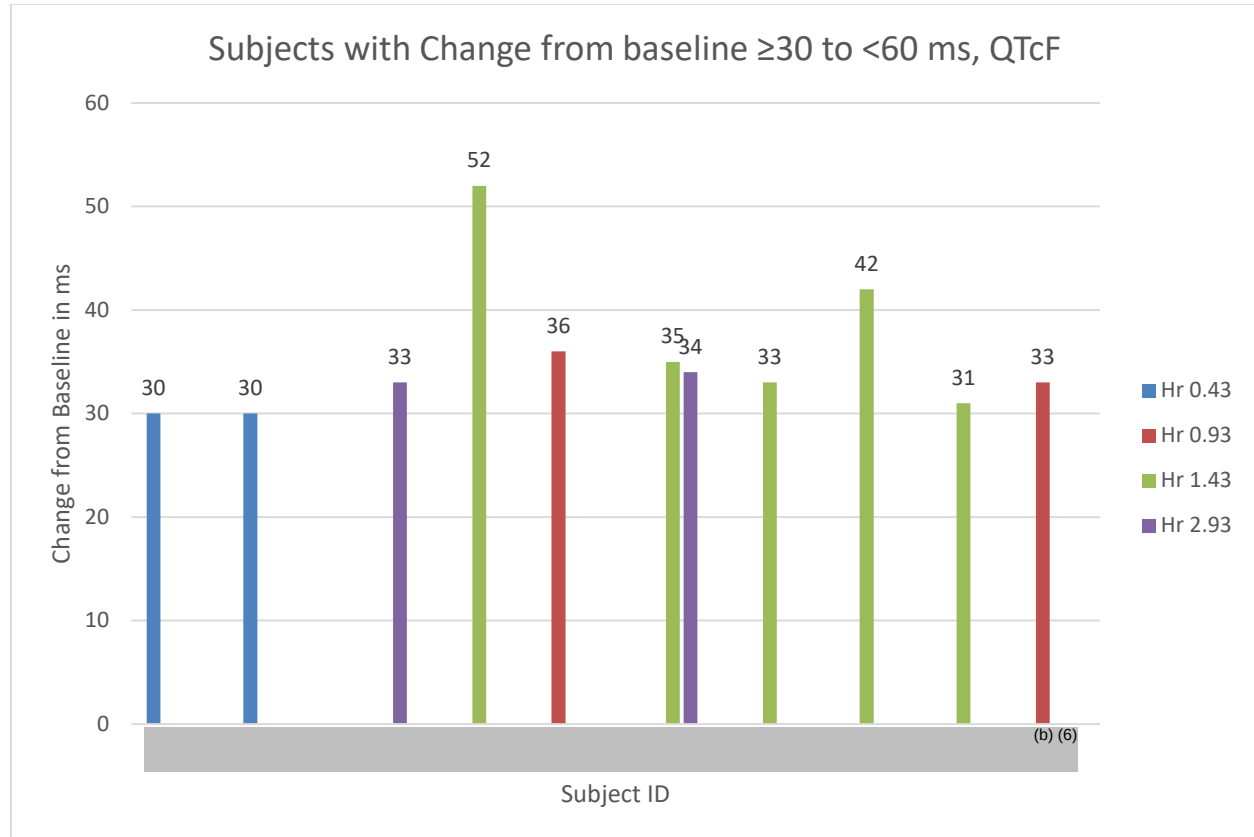
¹⁶ Gries RE, Brooks LJ. Normal oxyhemoglobin saturation during sleep: How low does it go. Chest. 1996;110:1489-1492.

QTcF values are subtracted from the 0.26, 0.43, 0.93, 1.43, 2.93, 5.93, 11.9-hour QTcF to obtain the change in QTcF from baseline to Xhr. These values are analyzed for mean change from baseline and to identify individual change from baseline. The maximum group mean change from baseline was 3.8ms. This occurred at 0.93 hours. There were 11 instances of change from baseline between 30 and 60 ms and two instances of a change greater than 60 ms. Nine of the QT increases > 30ms were less than 40ms while the remaining two were 52ms and 42ms, see [Figure 6](#). These occurred at 1.43 hours [Figure 6](#). There were two instances from two patients of QT interval increase greater than 60ms. The values were 64ms in patient (b) (6) and 60ms in patient (b) (6). The adverse event dataset for these two patients is examined. There are no cardiac adverse events. The only entries are somnolence and injection site pain.

Table 24 Study 1005, Group Mean Change from Baseline QTcF at 7 ECG Recording Times Post Midazolam 20mg by Autoinjector

Interval Post midazolam treatment	Group Mean Change from Baseline QTcF
0.26 Hr	2.2
0.43 Hr	3.4
0.93 Hr	3.8
1.43 Hr	-1.8
2.93 Hr	0.9
5.93 Hr	-6.6
11.9 Hr	-8.9

Figure 6 Study 1005, Instances of Change from Baseline QTcF, ≥ 30 to <60 by Patient and Time Post midazolam Injection



Post Baseline QTcF: Examination of post baseline QTcF was performed at hours 0.26, 0.43, 0.93, 1.43, 2.93, and 5.93. There were 20 instances from 12 patients where post baseline QTcF was greater than 450ms but less than 480ms and the baseline values was less than 450ms. The post dose intervals with maximum frequencies were 0.93 and 1.43 hours with 5 instances each. There was a single instance of a post dose QTcF value of 480ms at hour 0.93, there were no values greater than this entry.

Adverse Event Dataset: The RAMPART and MRP adverse event datasets are examined for ventricular dysrhythmia. Patient (b) (6) is identified with an event of "Torsade de pointes". This event occurred in a 75 yo male with end stage Parkinson's disease, diabetes, diabetic nephropathy, HTN, congestive heart failure and peripheral vascular disease with multiple toe amputations. The patient had a seizure associated with a serum glucose of 600mg/dl. The patient was enrolled in RAMPART and treated with IM midazolam. A subsequent glucose was 48mg/dl at reassessment) On ED arrival at 9:28am the patient had an interval of supraventricular tachycardia that was treated with cardio version. There was a second interval of atrial fibrillation with rapid ventricular response that required cardioversion. The patient had

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a third ECG in the ED after these events with a report of normal sinus rhythm with HR of 70, first-degree atrioventricular (AV) block, LBBB, left axis deviation, and non-specific ST segment/T wave abnormalities. Later in the day the patient had an episode of torsades rhythm resolved with cardioversion. On the following day a repeat ECG revealed sinus bradycardia (minimum heart rate 48 bpm) and sinus arrhythmia with first degree AV block, left anterior fascicular block, and left ventricular hypertrophy with repolarization abnormality.

Reviewer Comment: the concern in this case is the relationship of the episode of Torsade de pointes to the IM midazolam treatment. To the best that can be determined, the event occurred several hours following the T_{max} of midazolam. This event, also occurred in the context of a destabilizing medical event several hours earlier where supraventricular cardiac rhythm events required cardioversion. The underlying cardiac repolarization abnormality, seriously unstable metabolic state on arrival, a background of status epilepticus and a 1 to 2 half-life separation between the IM midazolam treatment and episode of Torsade de pointe make a causal relationship to midazolam very unlikely. The existing repolarization abnormality noted on ECG report on day 2 of hospital admission support this conclusion.

Medical Literature: Literature references are not in agreement on the effects of midazolam on the corrected QT interval. From among several clinical studies there were findings that ranged from no effect to a positive effect on prolongation of repolarization. A study on the specific effect of midazolam on hERG channel inhibition concluded *"midazolam might result in a small inhibition of hERG channels at therapeutic dosages. Thus, from a clinical point of view, pronounced effects on cardiac repolarization seem unlikely. These data correspond well to the reported and variable and rather small effect of midazolam on the QTc interval."*¹⁷

Reviewer Comment: A TQT study was not performed at original approval of midazolam in 1985. Analysis of the ECG data from study 1005 where IM midazolam was delivered at twice the dose of the RAMPART study, although not intended to be a TQT study, reveals small shifts to QT interval prolongation. In the above analysis ten patients (4%) have QTcF prolonged between 30 and 60ms but in eight of these the maximum change from baseline is +36 ms. There were 2 patients with prolongation over 60ms. The maximum group mean change from baseline at any post dose period up to 11.9 hours was 3.8ms. This is below the threshold of regulatory concern of 5ms in a formal QT study. There is extensive clinical experience in the use of midazolam in varying acute care medical circumstances including status epileptics. In status epilepticus the use of midazolam in the medical community is currently off label but is an accepted standard of

¹⁷ Vonderlin N, et. al. Anesthetic drug midazolam inhibits cardiac human ether-a-go-go-related gene channels: mode of action. Drug Design, Development and Therapy 2015;9 867–877. <https://www.dovepress.com/> by 150.148.14.135 on 30-Dec-2017

practice.^{18,19} This application addresses the same population as ongoing clinical use. Midazolam does not emerge as an agent that prolongs QT interval on examination of the medical literature.

8.4.10. Immunogenicity

N/A Midazolam is a small molecule

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Time to Seizure Cessation

The IM, IV treatment sequence directed by the RAMPART protocol was administration of IM autoinjector first followed by initiation of intravenous access and treatment. There is a longer latency to IV lorazepam deliver than IM midazolam delivery due to the process of obtaining IV access. However, this longer latency to medication delivery is partially offset by more rapid action of the direct intravenous lorazepam, see [Section 6.1.2, Seizure Termination](#).

8.5.2. Recurrent Status Epilepticus

Treatment Success patients in RAMPART with status epilepticus in the MRP follow up. The frequency of occurrence of status epilepticus during hospital follow up of RAMPART patients was higher as a percent of patients in the IV lorazepam treatment arm (5.6%) compared to the IM midazolam treatment arm (4.5%). The frequency as a proportion of successful outcomes was higher in the IV lorazepam arm (8.9%) than in the IM midazolam arm (6.1%), see [Table 25](#).

Table 25 Frequency of status epilepticus during MRP hospital follow up

Treatment arm	Treatment Success patients with SE in MRP	Successful outcome	Treatment arm n (ITT)	% successful outcome	% of patients in arm with SE	% of success with subsequent SE
IM	20	329	448	73.4	4.5	6.1

¹⁸ Glauser T, et.al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Currents*, Vol. 16, No. 1 (January/February) 2016 pp. 48–61.

¹⁹ Bauerschmidt, Andrew, Martin, Andrew and Claassen, Jan. Advancements in the critical care management of status epilepticus. *Current Opinion in Critical Care*, 23, 2, April 2017, 122–127. 10.1097/MCC.0000000000000392

Treatment arm	Treatment Success patients with SE in MRP	Successful outcome	Treatment arm n (ITT)	% successful outcome	% of patients in arm with SE	% of success with subsequent SE
IV	25	282	445	63.4	5.6	8.9

8.5.3. Respiratory compromise

RAMPART

The RAMPART adverse event dataset (adae.xpt) is examined for events in the SOC “Respiratory, thoracic and mediastinal disorders” for terms associated with ventilatory compromise. Preferred terms are also searched for “oxygen saturation decreased”. There were 12 preferred terms from the SOC “Respiratory, thoracic and mediastinal disorders” associated with ventilatory compromise. Ventilatory compromise is the pathologic state of interest due to the sedation / CNS depression that may reduce respiratory drive with midazolam treatment. These 12 terms are shown in [Table 26](#). Preferred term with a frequency greater than 1% in either the IM midazolam or IV lorazepam group are “Upper airway obstruction”, “respiratory depression” and “respiratory failure”. From among these terms there is a higher frequency of upper airway obstruction in the IM midazolam treatment arm than in the IV lorazepam arm. The frequency of “respiratory depression” and “respiratory failure” are greater in the IV lorazepam treatment arm. From among the remaining 9 terms with a frequency <1% six of the nine were more frequent in the IV lorazepam treatment arm. There were no entries for the preferred term “oxygen saturation decreased”. There was a higher frequency of terms associated with cardiorespiratory compromise in the IV lorazepam (31.1%) then in the IM midazolam (28.7%) treatment arm.

Table 26 RAMPART Study, Frequency of Ventilation dysfunction preferred terms from within the “Respiratory, thoracic and mediastinal disorders” SOC. IM compared to IV, ITT patient entries only in ADAE dataset.

Preferred term	IM	IV	IM %	IV %	1V% - IM%	0= IM > IV frequency
Upper airway obstruction	22	12	4.9	2.7	-2.2	0
Respiratory depression	19	29	4.2	6.5	2.3	1
Respiratory failure	7	16	1.6	3.6	2.0	1
Acute respiratory failure	2	2	0.4	0.4	0.0	1
Hypoxia	2	3	0.4	0.7	0.2	1
Tachypnea	2	0	0.4	0.0	-0.4	0
Apnea	1	1	0.2	0.2	0.0	1

Preferred term	IM	IV	IM %	IV %	1V% - IM%	0= IM > IV frequency
Respiratory arrest	1	0	0.2	0.0	-0.2	0
Respiratory distress	1	3	0.2	0.7	0.5	1
Dyspnoea	0	1	0.0	0.2	0.2	1
Hypoventilation	0	1	0.0	0.2	0.2	1
Obstructive airways disorder	0	1	0.0	0.2	0.2	1
Total	128	138	28.7	31.1	2.4	0

Reviewer Comment: Examination of respiratory safety events in the RAMPART adverse event dataset reveals an overall higher frequency of events associated with ventilatory dysfunction in the IV lorazepam group with a higher frequency of the high frequency terms “respiratory depression” and “respiratory failure” in the IV lorazepam group. There was a higher frequency of the term “upper airway obstruction” in the IM midazolam cohort, the reason for this is unclear.

MRP

Safety data from the hospital records of RAMPART patients was captured in the Medical Records Project. This data capture added to the available safety events from patient discharged directly from the hospital emergency department (RAMPART0 after treatment of status epileptics and provides additional follow up safety data on patients who were admitted to the hospital from the emergency department.

The sponsor included an “Acute Central Respiratory Depression” modified standardized MedDRA query (SMQ), see [Appendix](#)

Examination of the MRP, ADSE (adverse safety events) for all patients (including repeat enrollments) for patients with an “Acute Central Respiratory Depression” modified SMQ flag is performed. There are 14 preferred terms captured from more than a single patient in the IM midazolam treatment group. The frequency of unique patients with these corresponding terms in the IV lorazepam treatment arm is compared. Total patient enrollment (by treatment arm) is used as the denominator. The most frequently occurring adverse event term is “respiratory failure” with a frequency in the IM midazolam and IV lorazepam groups of 9.5% and 13.2% respectively. The next most frequent preferred term event is “acute respiratory failure” where the frequency in the IM midazolam and IV lorazepam were 5.3% and 6.9% respectively. The remaining 12 terms have small differences in the number of unique patient events between treatment arms and conversion to percent differences amplifies the actual patient frequency, see [Table 27](#).

Table 27 MRP , Respiratory SMQ Term Comparison, IM midazolam to IV lorazepam, All Patient ADSE dataset

	Total IM midazolam n = 514		Total IV lorazepam n = 509	
preferred term	IM midazolam # Patients	IV lorazepam # Patients	IM %	IV %
RESPIRATORY FAILURE	49	67	9.5	13.2
ACUTE RESPIRATORY FAILURE	27	35	5.3	6.9
DYSPNOEA	16	14	3.1	2.8
RESPIRATORY DISTRESS	12	10	2.3	2.0
CARDIAC ARREST	5	2	1.0	0.4
HYPOXIA	5	5	1.0	1.0
APNOEA	3	1	0.6	0.2
RESPIRATORY ARREST	3	1	0.6	0.2
CARDIO-RESPIRATORY ARREST	2	1	0.4	0.2
CYANOSIS	2	2	0.4	0.4
HYPOPNOEA	2	0	0.4	0.0
RESPIRATORY DEPRESSION	2	2	0.4	0.4
RESPIRATORY DISORDER	2	0	0.4	0.0
RESPIRATORY ACIDOSIS	0	4	0.0	0.8
Total respiratory SMQ Events (all terms including n=1 patient)	121	134	23.5%	26.3

Reviewer Comment: Examination of the MRP ADSE dataset for all patients reveals a small excess of respiratory compromise events in the IV lorazepam group where the most frequent two terms are “respiratory failure” and “Acute respiratory failure”, both more frequent in the IV lorazepam treatment arm. There is no evidence of an increase in respiratory compromise in the IM midazolam treatment arm. See discussion integrating findings in healthy volunteers and RAMPART patients in the [conclusion](#) of the respiratory compromise section.

Healthy Volunteers

STUDY 11903 (single dose, escalation 0.1mg/kg to 0.49mg/kg six steps, 6 patients /group)

There is a dedicated dataset for respiratory depression entries (drespeva.xpt). No respiratory depression reported in the dataset although the adverse event dataset (dae.xpt) has an entry

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for a single subject with O₂ saturation by pulse oximetry of 89% for < 1 minute. This subject was in the 0.25mg/kg dose group and received 15mg of midazolam using one 5mg and one 10mg autoinjector. Examination of the 0.49mg/kg dose group reveals a minimum O₂ saturation of 94% on day 0.

Study 1001, n=24: 10mg autoinjector x 2 separated by 1min or 10 min, 2-way, randomized sequence, open-label, crossover with 1 day between periods).

Examination of the respiratory depression dataset (dresaa.xpt) reveals 3 (12.5%) subjects ((b) (6)) with events of respiratory depression. Two of these events were in the treatment sequence of 2 x 10mg midazolam autoinjector separated by 10 minutes and one in the separation by less than one minute. The duration of the respiratory depression events in the three subjects were 8:26, 8:39 and 8:37 respectively in minutes: seconds. Treatment in two instances were tactile/verbal stimulus and in the third a chin lift. Corresponding O₂ saturations for the three subjects were 74%, 87% and 78%.

Examination of the vital sign dataset (dvitaa.xpt) identifies a minimum O₂ saturation of 90. The low values for subjects identified above are not in the vital signs dataset.

Examination of the adverse event dataset reveals 3 events of the preferred term “respiratory depression” and one event of “apnea”. These 4 instances occur in 3 subjects (13%) ((b) (6)) corresponding the entries in the respiratory depression dataset discussed above.

Study 1002, n= 24: TRT A-10mg autoinjector x 2 separated by 1min, TRT B- Atropine 2.0 mg auto-injector followed 10 min later by midazolam 2 x 10 mg auto-injectors administered <1 min apart 2-way, randomized sequence, open-label, crossover with 1 day between periods).

Examination of the respiratory depression dataset (dresaa.xpt) identifies no events of respiratory depression. Examination of the vital sign dataset reveals one (4.2%) O₂ saturation entry less than 91%. This event is an O₂ saturation of 80% (client ID # (b) (6)). This occurs during treatment sequence A (2 x 10 mg midazolam auto-injectors separated by < 1 minute). Examination of the adverse event dataset (daepaa.xpt) dataset does not identify any entries in the “Respiratory, thoracic and mediastinal disorders” SOC. There are two subject (8.3%) entries (client ID # (b) (6)) in the SOC “investigations”. These occur as the preferred terms “oxygen saturation decreased”. These occur in treatment sequence B “1 x 2 mg atropine sulfate followed 10 minutes later by 2 x 10 mg midazolam auto-injectors separated by < 1 minute (Test)”

Study 1003, n= 24: TRT A-10mg autoinjector x 2 separated by 1min, TRT B- Atropine

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(2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL), combined in a single auto-injector followed by midazolam 2 x 10 mg auto-injectors administered <1 min apart, 2-way, randomized sequence, open-label, crossover with 1 day between periods).

Examination of the respiratory depression dataset (dresaa.xpt) identifies no events of respiratory depression. Examination of the vital sign dataset reveals a single entry minimum O2 saturation of 90% . Examination of the adverse event dataset (daepaa.xpt) dataset reveals no entries in the “Respiratory, thoracic and mediastinal disorders” or “investigations” SOC’s.

Study 1004, n= 24: TRT A-10mg autoinjector x 2 separated by 1min, TRT B- Oral pyridostigmine (30 mg) followed 120 min later by atropine (2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL) by auto-injector followed by midazolam 2 x 10 mg auto-injectors administered <1 min apart, 2-way, randomized sequence, open-label, crossover with 1 day between periods).

Examination of the respiratory depression dataset (dresaa.xpt) reveals one subject (ID# (b) (6)) (4.1%) with an entry of respiratory depression for both treatment sequences. Both identify the time of event at 8:59 post injection lasting 15 seconds. The events are treated in period 1 with “PILLOW REMOVED, JAW LIFTED, AND SUBJECT STIMULATED” and in period 2 with repositioning. Oxygen saturation at the time of event in period one was 88% and in period 2 it was 85%. Examination of the vital sign dataset reveals three entries from two subjects (8.3%) of O2 saturation less than 91% (ID # (b) (6)). Subject (b) (6) has an entry of 79%. Subject (b) (6) who also had an entry of respiratory depression had entries of 84% and 89%. Examination of the adverse event dataset (daepaa.xpt) reveals two entries in the SOC “Respiratory, thoracic and mediastinal disorders” and none in the “investigations” SOC. The preferred term entries in the “Respiratory, thoracic and mediastinal disorders” SOC were both “hiccups”. There were no respiratory insufficiency entries.

Study 1005, n= 250: Study to evaluate safety of IM midazolam autoinjector. 2 x 10 mg auto-injections administered <1 min apart. Single dose study.

Examination of the respiratory depression dataset (dresaa.xpt) reveals 11 instances of respiratory depression from two subjects (0.8%) (clientid (b) (6)). Subject (b) (6) had 4 entries with a minimum O2 saturation of 84% and a minimum respiratory rate of 2 breaths per minute. In two instances the duration of event is not provided in the remaining two events the duration is 15 second in each. The interventions included “verbal tactile stimulation”, “verbal stimuli”, “repositioning” and “jaw lift”. Subject (b) (6) entries with a minimum respiratory rate of 0 and a minimum O2 saturation of 74%. Duration of the respiratory depression events ranged from a maximum of 42 seconds to a minimum of 5 seconds. Interventions included “subject awakened to breathe” and “subject stimulated to breathe”.

Examination of the vital sign dataset reveals 4 instances from 4 (1.6%) subjects of O2 saturation less than 90%. Subjects (b) (6) had O2 saturation values of 60, 78, 89, and 89 respectively. Subject (b) (6) had 15 O2 saturation entries with one abnormal entry of 78% saturation at 0.48 hours post midazolam dose. Subject (b) (6) had 15 O2 saturation entries where all were >91% except at 1.48 hours post midazolam dose where saturation was 89%. Baseline saturation was 99%. Subject (b) (6) had 16 O2 saturation entries where baseline was 99% and all were > 94% except 167.8 hours post midazolam dose. Subject (b) (6) had 16 O2 saturation entries with a baseline of 99% with all > 91% except for an entry of 89% at 0.15 hours post midazolam dose.

Examination of the adverse event dataset (daepaa.xpt) revealed 30 entries from 26 subjects in the SOC “respiratory, thoracic and mediastinal disorders” and 22 entries from 14 subjects in the SOC “investigations”. From among the 30 entries in the “respiratory, thoracic and mediastinal disorders” there were 9 (3.6%) subjects with a preferred term entry for “Hiccups” and 3 (1.2%) patients with a preferred term entry for “respiratory depression”. None of these was entered as an SAE. From among the 14 subjects with entries in the SOC “investigations” 13 (5.2%) subjects had a preferred term entry of “oxygen saturation decreased” and one (0.4%) of these subjects had a second entry for “respiratory rate decreased” and one for “oxygen saturation decreased”. None was entered as an SAE.

Summary: in the smaller healthy volunteer studies 1001, 1002, 1003, and 1004 up to 13% of subjects had events of respiratory depression, up to 8% of subjects had an event of oxygen saturation less than 90% and up to 8% had adverse event term entries associated with respiratory dysfunction. In study 1005 a large study of 250 healthy volunteers treated with 20 mg midazolam delivered by autoinjector as two 10mg injections in < 1 minute 0.8% of subjects had entries in the respiratory depression dataset while 1.6% of subjects had vital sign entries with oxygen saturation less than 90% and 1.2% of subjects had adverse event term entries for “respiratory depression” with 5.3% of subjects there was an entry for “Oxygen saturation decreased”. From among the events of respiratory depression all were resolved with simple physical intervention or increased stimulus. There was no instance where positive pressure ventilation by any means was needed. The events of oxygen saturation less than 90% were generally short and did not require advanced life support intervention. None of the adverse event term entries for respiratory compromise were flagged as SAEs.

Reviewer Comment: Examination of the healthy volunteer response to 20mg IM midazolam dosing reveals events of compromised ventilatory function in up to 10% of subjects. No interventions of advanced life support were required. Auditory stimulus and or physical stimulation was sufficient to resume ventilation.

Respiratory Compromise Conclusion

Respiratory failure is a complication in one third of status epilepticus episodes.²⁰ Examination of adverse events associated with ventilatory compromise / respiratory failure in the RAMPART study and MRP revealed a higher frequency of respiratory compromise events in the IV lorazepam treatment arm. The maximum frequency of total respiratory compromise events of all preferred term in the IV lorazepam and IM midazolam treatment arms were 26.3% and 23.5% respectively. These frequencies do not exceed the frequency of 33% respiratory failure in status epilepticus events that is reported in the medical literature. Review of the adverse events in the PK and safety study of healthy volunteers who received twice the dose (20mg) of midazolam as patients in the RAMPART study did not identify any events that required measures of advance life support such as positive pressure ventilation of any means either with a bag valve mask apparatus or mechanical ventilation. This difference between healthy volunteers and status epilepticus patients is evidence that the primary driver of ventilatory compromise / respiratory failure in the status epilepticus cohort is the sustained seizure more than adverse benzodiazepine drug effect. The IV lorazepam had a higher frequency of overall respiratory events than the IM midazolam by a small margin. This provides assurance there is no unexpected mechanism to cause respiratory compromise with the use of IM midazolam.

8.5.4. Renal Dysfunction

RAMPART

All Events, Including Repeat Enrollment

There were 22 unique patient events from both treatment arms. These events are shown in [Table 28](#). The most frequent event term is “renal failure acute” identified in 11 (2.1%) patients in the IM midazolam arm and 5 (1.0%) patients in the IV lorazepam arm while the next most frequent event in the IM midazolam arm was “renal failure” that occurred in 3 (0.6%) patients while there were no occurrences in the IV lorazepam arm. The remaining events occurred in a single patient each.

Table 28 Renal Dysfunction Events from All AE Entries (includes repeat enrollment)

	Midazolam (n=514)		Lorazepam (n=509)	
Preferred term	IM Patients	% IM entries (n=514)	IV patients	% All IV entries (n=509)
Renal failure acute	11	2.1	5	1.0

²⁰ Hawkes MA, Hocker SE. Systemic Complications Following Status Epilepticus. Current Neurology and Neuroscience Reports 2018;18.3. Hawkes MA, Hocker SE. Systemic Complications Following Status Epilepticus. Current Neurology and Neuroscience Reports 2018;18.

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Renal failure	3	0.6	0	0.0
Blood creatinine increased	1	0.2	0	0.0
Urine output decreased	1	0.2	0	0.0
Nephropathy toxic	0	0.0	1	0.2

ITT Only

Analysis of adverse events related to renal dysfunction is performed on events only from the ITT population that does not contain repeat enrollments. Patients in this subset may not have had a renal dysfunction event on first enrollment but could have an event on a repeat enrollment that would not be captured in this subset. They would be captured in the analysis above, on all patient adverse event entries.

There were 20 unique patient events from both treatment arms. These events are shown in [Table 29](#). The most frequent event term is “renal failure acute” identified in 9 (2.0%) patients in the IM midazolam arm and 5 (1.1%) patients in the IV lorazepam arm while the next most frequent event in the IM midazolam arm was “renal failure” that occurred in 3 (0.7%) patients in the IM midazolam arm while there were no occurrences in the IV lorazepam arm. The remaining events occurred in a single patient each.

Table 29 Renal Dysfunction Events from ITT Population AE Entries

Preferred term	Midazolam		lorazepam	
	IM	% IM	IV	% IV
Renal failure acute	9	2.0	5	1.1
Renal failure	3	0.7	0	0.0
Blood creatinine increased	1	0.2	0	0.0
Urine output decreased	1	0.2	0	0.0
Nephropathy toxic	0	0.0	1	0.2
TOTAL	14		6	

Deaths in Renal Dysfunction

There were five deaths among the 20 patients in the RAMPART ITT cohort with renal dysfunction terms, 3 in the IM midazolam group and 2 in the IV lorazepam group. All were admitted directly to the ICU and none were intubated during transit.

Reviewer Comment: there is a higher frequency of “Renal failure acute”, “Renal Failure” and “Blood creatinine increased” in the IM midazolam treatment arm than in the IV lorazepam treatment arm. There were 5 deaths among the patients with a renal dysfunction adverse event term where 3 of 5 occurred in the IM midazolam treatment arm and 2/5 in the IV lorazepam arm. The inequality between frequency of deaths is smaller than the inequality of all renal

dysfunction event terms between treatment arms. The basis for the inequality between treatment arms will be explored further from data in the MRP safety dataset. The MRP dataset will provide follow up information from addition capture of medical record data and from hospital charts of those patients who had hospital admission. The MRP dataset will also identify addition patients in the study population that develop renal dysfunction safety events as well as their medical outcome.

MRP

All Enrollments

There were 22 patients in the RAMPART adverse event dataset with renal dysfunction terms. All are included in the MRP Renal Failure SMQ, see next paragraph. Twenty of the 22 RAMPART patients with renal failure terms are identified in the MRP ADSE (adverse safety events) dataset. Two patients, SUBJID (b) (6) are not carried forward into the MRP ADSE dataset. No reason is identified Neither patient has death reported. They are both identified as hospital discharge. The renal failure adverse events are identified as resolved and were not flagged as SAEs. All 5 deaths in the RAMPART adverse event dataset associated with a renal failure SMQ term are also identified in the MRP, ADSE dataset.

The MRP ADSE (adverse safety events) dataset contains a flag for renal dysfunction events. This flag is based on an [“Acute Renal Failure” SMQ](#) based on MedDRA version16. There were 113 instances of a positive flag from 108 unique patients. From among these patients there were 54 (11%) from the IM midazolam treatment arm and 54 (11%) from the IV lorazepam treatment arm. Three of the 54 IM midazolam patients were in the low dose group while 1 of the IV lorazepam patients was from the low dose group, see [Table 31](#). There were equal numbers of Acute Renal Failure SMQ adverse safety events in the IM midazolam and IV lorazepam treatment arms.

The relationship between acute renal failure SMQ entries and time to seizure cessation is examined. There were 108 patients with a renal failure SMA adverse safety event term in the MRP dataset. From among these were 68 with a value for time to seizure cessation. The mean and median time to cessation for this group were 415.2 and 295 seconds respectively. In the 925 remaining patients without a renal failure adverse safety event there were 602 with a value for time to seizure cessation, see [Table 30](#). The mean and median time to cessation for this group were 409 and 312 seconds respectively. There is no evidence of a relationship between the duration of status epileptic until termination and occurrence of a renal failure SMQ.

Table 30 All Enrollments, Acute Renal Failure SMQ Status and Time to Seizure Cessation

	Time to Seizure Cessation
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ACUTE RENAL FAILURE SMQ	Sz Cessation Time Entry YES=1, NO= 0 2	# Patients	Mean	Median
N	0	313	No time entries present	
N	1	602	408.9	311.5
Y	0	40	No time entries present	
Y	1	68	415.2	295

Table 31 MRP, All Patients with Acute Renal Failure SMQ Flag, by Treatment Arm and Dose Tier

	Midazolam	Lorazepam	Midazolam	lorazepam	
Treatment tier	# IM	# IV	% IM	% IV	
Low	3	1	5.6	1.9	% Patients with Renal Flag
High	51	53	94.4	98.1	
All	54	54	10.5	10.6	% of total treatment arm

The frequency of death in the population with a renal failure flag in the ITT population is examined. There were 3 (0.7%) deaths in this cohort in the IM midazolam treatment arm and 7 (1.6%) deaths in the IV lorazepam treatment arm.

ITT Population

The frequency of renal failure flag based on the Acute renal failure SMQ was examined in the ITT population of the MRP adverse safety event dataset. There were 105 instances of a positive flag from 100 unique patients. From among these patients there were 48 (11%) from the IM midazolam treatment arm and 52 (12%) from the IV lorazepam treatment arm. Three of the 45 IM midazolam patients were in the low dose group while 1 of the IV lorazepam patients was from the low dose group, see [Table 32](#).

Table 32 MRP, ITT Patients with Acute Renal Failure SMQ Flag, by Treatment Arm and Dose Tier

	Midazolam	Lorazepam	Midazolam	lorazepam	
Treatment Tier	# IM	# IV	% IM	% IV	
Low	3	1	6.3	1.9	% Patients with Renal Flag
High	45	51	93.8	98.1	
Total	48	52	10.8	11.7	% of total treatment arm

The frequency of death in the population with a renal failure flag in the ITT population is examined. There were 3 (0.7%) deaths in this cohort in the IM midazolam treatment arm and 7

(1.6%) deaths in the IV lorazepam treatment arm. There is no difference in the frequency of death or distribution across treatment arms in this examination between the total patient cohort and the ITT cohort, all deaths occurred in the ITT population in the high dose treatment group whether in the IM midazolam or IV lorazepam treatment group. Eight of the 10 patients with death and a renal failure adverse event term also had an instance of intubation. Three of the eight patients with an entry for endotracheal intubation were in the IM midazolam arm with 5 were in the IV lorazepam arm. The time to seizure cessation is available for 5 of those eight patients who were intubated. Seizure cessation time ranged from 238 (4min) to 667 (11.1 min) seconds with a mean and median of 478 seconds and 442 seconds respectively. From among all patients including repeat enrolment there were 674 with measurements for time to seizure cessation. The overall mean and median time to seizure cessation were 410 and 308 seconds respectively. There is a notably longer time to seizure cessation among the 8-intubated patient with a fatal outcome and a renal failure SMQ when compared to the time to cessation among all enrolments.

Safety Events; Patients with Renal Failure SMQ terms Compared to those Without Renal SMQ Safety Events

An assessment of the broad medical status of the patients with a renal failure SMQ term compared to the patients without a renal failure term may provide some insight into the basis for a renal failure event among patients All patient entries, including repeat enrollment of the MRP ADSEALL.xpt dataset is examined to compare the top ten preferred terms of the 108 patients (*both treatment arms combined*) positive for a renal failure SMQ term to the frequency of those terms in the 915 patients without a renal failure SMQ term. For the remaining discussion, the terms “patients with a renal failure SMQ term” will be abbreviate “positive SMQ” while patients “without a renal failure SMQ term” will be abbreviated “SMQ negative”.

This analysis reveals the top preferred term among the patients with a renal failure term is “respiratory failure”. 28% of renal failure SMQ patients have a “respiratory failure” adverse event where 9.4% of non-renal failure SMQ patients have and entry for this adverse event. This is likely a marker for a more serious status epilepticus event or a more vulnerable underlying medical status. There are 4 additional terms that suggest the patients with a renal failure SMQ term have a more severe disease course associated with their event of status epilepticus. The frequency of “hypotension” is 5 times greater in the positive SMQ group. The term “acute respiratory failure” is 4 times more frequent while “anemia” is 6 times as frequent in the positive SMQ group. Most noteworthy is the term “rhabdomyolysis” where the frequency is 44 times greater in the positive SMQ group with absolute frequencies of 24 unique patient events in the positive SMQ group and 5 unique patient events in the much large SMQ negative group.

Table 33 MRP, Frequency of Top Ten Preferred Terms of the Renal Failure SMQ Cohort Compared to the Frequency of the Same Terms in those without a Renal Failure SMQ Term (from all patients, ADSEALL.xpt).

Preferred Term	# patients with renal failure SMQ term (total n= 108)	# patients without a renal failure SMQ term (total n= 915)	% of patients with renal failure SMQ term	% patients without a renal failure SMQ term	multiple of renal failure negative patients
ACUTE KIDNEY INJURY*	80		74.1		
RESPIRATORY FAILURE	30	86	27.8	9.4	3.0
HYPERTENSION	27	39	25	4.3	5.8
HYPOTENSION	26	44	24.1	4.8	5.0
STATUS EPILEPTICUS	26	111	24.1	12.1	2.0
POSTICTAL STATE	24	151	22.2	16.5	1.3
RHABDOMYOLYSIS	24	5	22.2	0.5	44.4
HYPOKALAEMIA	23	71	21.3	7.8	2.7
ACUTE RESPIRATORY FAILURE	21	41	19.4	4.5	4.3
ANAEMIA	21	31	19.4	3.4	5.7
HYPERNATRAEMIA	21	6	19.4	0.7	27.7
SEIZURE	20	125	18.5	13.7	1.4
* Acute Kidney Injury is an SMQ search term used to differentiate the cohorts, therefore it cannot be present in the non-renal SMQ term cohort.					

A potential cause of rhabdomyolysis is muscle contraction during a seizure. The high frequency seen in [Table 33](#) may be due to a difference in the intensity of muscle contraction, the total volume of muscle recruited during a seizure or the duration of a seizure. Metrics to differentiate intensity or overall amount of muscle recruited in a seizure were not captured by the study. Time to seizure cessation was captured and can be examined to determine if there is a difference in duration of seizure between those with rhabdomyolysis compared to those patients without this preferred term. In this analysis, the time to seizure cessation, by treatment arm, of the 24 patients with preferred term rhabdomyolysis is compared to the time to seizure cessation of the patient cohort who are SMQ negative (n=915), by treatment arm.

This analysis reveals the 17 patients in the IM midazolam cohort with a “rhabdomyolysis” preferred term entry have a longer mean and median latency to cessation of seizure than the mean and median latency for the IV lorazepam treatment arm. The IM midazolam arm has a longer mean and median latency by 76 and 108 seconds respectively, [Table 34](#). As noted in the discussion in [section 6.1.2, seizure termination](#), entries for time to seizure cessation are not provided for all patients. From among the 17 patients with “rhabdomyolysis” in the IM midazolam group there were 12 with time to seizure cessation entries while from among the 7

patients in the IV lorazepam arm with “rhabdomyolysis” there were 5 with time to seizure cessation entries.

Examination of the SMQ negative cohort reveals that 67% of the IM midazolam treatment cohort had a time to seizure cessation entry while 64% of the IV lorazepam cohort had a time to cessation entry. The mean and median time to cessation were shorter for the IM midazolam cohort by 66 and 53 seconds respectively, [Table 34](#). This observation is reverse of the small positive SMQ patient cohort with a “rhabdomyolysis” preferred term entry where the IM group had longer latency to seizure cessation. This analysis reveals there is a small subset of IM midazolam treated patients with time to seizure cessation longer than the more typical patient in the IM midazolam cohort. This longer duration of seizure was sufficient to result in muscle damage with rhabdomyolysis. Within this cohort of 17 there were 13 (76%) outcome successes while in the IV lorazepam cohort with “rhabdomyolysis” there were 2 (28%) successful outcome patients.

Reviewer Comment: A subset of the positive SMQ (renal) cohort had rhabdomyolysis that may account for renal injury (note the renal SMQ terms do not capture rhabdomyolysis). Within this subset those patients in the IM midazolam cohort had a longer latency to seizure cessation than the IV lorazepam cohort with rhabdomyolysis. This relationship is opposite that of the larger study population that is SMQ negative where the IM midazolam cohort has a shorter latency to seizure cessation (by group mean and median) than the IV lorazepam cohort. From among the small cohort with “rhabdomyolysis” the IM midazolam retains a notably higher treatment success rate. The observation that this subset of IM midazolam patients with longer latency to seizure cessation is small group and retains a high treatment success rate supports the benefit of IM midazolam treatment of status epilepticus over IV lorazepam.

Table 34 MRP, “Rhabdomyolysis Cohort vs Negative Renal SMQ Cohort Group Mean and Median Time to Seizure Cessation by Treatment Arm. (all patients, including repeat enrollment, ADSEALL dataset)

	"rhabdomyolysis" cohort, n=24			Negative renal SMQ term, n= 915		
Treatment arm	# patients*	mean	median	# patients†	mean	median
IM Midazolam	17	472	403	460	377	286
IV Lorazepam	7	397	295	455	443	339
Difference in latency By treatment arm		76	108		-66	-53
* 71% of patients had time to cessation entry						
† 66% of patients had time to cessation entry						

An analysis of the 10 most frequently occurring preferred terms in the positive SMQ group by treatment arm was performed for examination of differentiating features. The most frequently occurring preferred terms in the IM midazolam treatment arm are compared to the corresponding terms for the IV lorazepam treatment arm. The comparator of interest is the IM midazolam treatment arm; therefore, the 10 most frequent terms of the IV lorazepam arm differ. The IM midazolam treatment arm is the independent variable while the IV lorazepam treatment arm is dependent on the terms identified from the IM examination. There are two most notable differences between the treatment arms. The term “rhabdomyolysis” occurs 2.4 times more frequently in the IM midazolam while the term status epilepticus occurs twice as frequently in the IV lorazepam arm, see [Table 35](#).

Table 35 MRP, Frequency of Top Ten Preferred Terms from the IM midazolam Treatment Arm Compared to the Corresponding Terms for IV lorazepam Arm. Renal Failure SMQ Cohort (from all patients, ADSEALL.xpt).

	IM midazolam positive renal SMQ total n= 54		IV lorazepam positive renal SMQ , n= 54			
Preferred term	IM Midazolam patients with term	% of IM	IV lorazepam patients with term	% IV	difference between percent	IM multiple of IV
ACUTE KIDNEY INJURY	40	74.1	40	74.1	0.0	1.0
RHABDOMYOLYSIS	17	31.5	7	13.0	18.5	2.4
HYPOTENSION	15	27.8	11	20.4	7.4	1.4
RESPIRATORY FAILURE	15	27.8	15	27.8	0.0	1.0
HYPERTENSION	14	25.9	13	24.1	1.9	1.1
ANAEMIA	12	22.2	9	16.7	5.6	1.3
ACUTE RESPIRATORY FAILURE	11	20.4	10	18.5	1.9	1.1
HYPERNATRAEMIA	11	20.4	10	18.5	1.9	1.1
POSTICTAL STATE	11	20.4	13	24.1	-3.7	0.8
SEIZURE	11	20.4	9	16.7	3.7	1.2
STATUS EPILEPTICUS	9	16.7	17	31.5	-14.8	0.5

Reviewer Comment: the observation of a multiple of approximately 2, in opposite directions for “rhabdomyolysis” and “status epilepticus” respectively is consistent with the identification of a longer latency to seizure cessation than the mean for SMQ negative patients while the IM midazolam retains an advantage by the occurrence of fewer adverse safety event entries for “status epilepticus”

Deaths

There were 10 deaths (included in section 8.4.1 Deaths) among the 108 patients in the MRP with a renal failure SMQ terms, three (30%) of these patients were in the IM midazolam

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treatment arm and 7 (70%) were in the IV lorazepam cohort. The patient case report narratives were examined to determine the relationship between the fatal outcome and the renal failure SMQ term. Review of the report details reveals there was no relationship between the medical complications that resulted in death and the renal failure event terms for any of these 10 patients. In all instances the renal failure SMQ event was an epiphenomenon of the serious challenging overarching medical disorders that accompanied the event of status epilepticus that allowed entry into the study or were complications resulting from the status epilepticus. Narrative synopses are presented in [Table 36](#).

Table 36 Narrative Synopsis and Conclusion on Relationship of Renal Function Term to Death in 10 Patients with Renal Failure SMQ Term and Fatal Outcome (included in section 8.4.1 Death)

SUBJID	Treatment	Death Review	Conclusion, related to RF
(b) (6)	4mg lorazepam in narrative, high dose in ADCR dataset	60yo B female, Underlying CKD, CV disease, seizure onset after sleeping?, received assigned study drug lorazepam and midazolam. Treatment failure due to rescue med but not seizure in ER. Hypoxemia on arrival to ER pCO2 67, required PEEP, BP 254/136 with subsequent drop to 88/55. Non-ST elevation MI Troponin 1.89. 4 days post admission multiple cerebral infarcts with hemorrhagic component. Positive sub-falcine shift. Death 4 days post admission.	RF SMQ due to underlying severe multiorgan compromise. 2 nd event.
	10mg midazolam	59 yo B male, no seizure history. Parkinson's disease, ETOH abuse, CAD, Anemia, HTN, DM. no Seizure on ED arrival. CT brain unrevealing. Creatinine 1.2. Glucose 177. Coagulopathy due to underlying sepsis. Chest X ray revealed retrocardiac atelectasis or infiltrates. Dx acute tubular necrosis on day 2 creatinine 1.7mg/dl. enterococcal bacteremia sepsis on day 4 after arrival. Day 7 after admission, pneumonia, disseminated intravascular coagulation. Death 64 days after admission	Death due to underlying medical compromise, development of sepsis, multiorgan failure. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	IV lorazepam low dose	74 yo Female, history of renal transplant, stage 2 colon cancer. Severe peripheral vascular disease. No seizure on arrival to ER. Complex medical course after admission, death from septic shock (persistent enterococcal bacteremia), death 58 days after admission	Death due to underlying medical compromise, development of sepsis, multiorgan failure. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	IM midazolam 10mg	67 yo w female. Medical history: partial tumor resection at the level of pons, hydrocephalus, multiple vasculo-peritoneal shunt placements. On arrival to ED seizures continue Subsequent multiple doses of lorazepam with resulting respiratory failure. Troponin was 3.77 and the subject was diagnosed with non-ST segment elevation myocardial infraction. CK 7679, BP 77/62, improved with fluid resuscitation. Pseudomonas pneumonia 9 days after admission. Unremitting seizure throughout the hospitalization. Death 29 days after admission	Patient had severe CKD at admission. Death due to unremitting seizures, underlying medical compromise. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	IV lorazepam 4mg.	62 yo B female, no seizure history. Medical history: pertinent medical history of pituitary macroadenoma with transsphenoidal	Death due to large intracerebral

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		hypophysectomy, gamma knife stereotactic radiosurgery, panhypopituitarism, hydrocephalus, ventriculo-peritoneal shunt placement, depression, encephalopathy, shock, respiratory distress, unspecified chest pain, nephrolithiasis with lithotripsy, chronic kidney disease, recurrent urinary tract infections, hypertension, anemia, thrombocytopenia, pancytopenia, chronic pancreatitis, diabetes mellitus, diabetes insipidus, hypoglycemia, hyponatremia, chronic pain syndrome, hypothermia, gait instability, septicemia, abscess and cellulitis of the foot, hepatitis C, alcohol abuse, and obesity. On arrival to ED no seizures Intubated due to respiratory failure. SE resumed. CT revealed large intracerebral bleed. BP 53/32. Dx septic shock. Patient had fluid and pressor resuscitation with BP improvement to 101/57. Death occurred 7 days after admission when life support withdrawn.	hemorrhage and cerebral hypoxia. RF SMQ term is a secondary event and did not result directly from medication or treatment method
(b) (6)	IV lorazepam 4mg	53 yo B female, Medical history of multiple strokes, dementia, CHF, COPD, DM type 2, HTN cocaine abuse. Upon ED arrival SE was ongoing. Respiratory failure and respiratory acidosis. BP 82/58. Creatinine 1.88. Day 2 patient had EEC consistent with partial SE of left hemisphere. Pt in burst suppression EEG 2 days after admission. On day 4 found to have pancytopenia, Hgb 7.7 g/dl continued to drop from admission and pt received second of two blood transfusions (4 units total).	Death due to continued status epilepticus and underlying medical compromise leaving patient unable to tolerate the stress of sustained SE and resulting treatment. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	IV Lorazepam 4mg	84 yo Asian female, pertinent MH: subdural hemorrhage, dementia, hypertension, rectal cancer, pneumonia. cachexia, malnutrition, chronic hypokalemia, chronic anemia, possible peritonitis. Upon ED arrival no seizures. Seizure later recurred with lorazepam treatment and respiratory failure. Blood cultures revealed enterococcal septicemia. CXR revealed CHF, left pleural effusion wit possible pneumonia. BP 90/55 with hypokalemia, hypomagnesemia, anemia (day 2) hb 6.8g/dl. effusion. Twenty-four hours post admission, she was only flexing to pain with no verbalization. 1 st day post admission creatinine 0.8mg/dl with BUN 3mg/dl. Life support withdrawn with death on day 4 post admission.	Death due to underlying medical compromise, development of sepsis, multiorgan failure. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	Assigned Im midazolam 10mg (not delivered)	53 yo B male. Pertinent medical history: laryngeal carcinoma surgery, left hilar calcified granuloma, delirium tremens, alcohol abuse, congestive heart failure, hypertension, hypothyroidism. Upon arrival to ED seizure continued. Patient treated in transit only with rescue diazepam. After arrival treated with lorazepam and phenytoin. Also in respiratory failure and was intubated. CT head revealed large intraparenchymal bleed. No midline shift. Hypertension on admission, max reading 220mmHg systolic. Max diastolic 170mmhg. Creatinine on admission 2mg/dl. Underlying cerebral hemorrhage enlarged with midline shift. 7 days after admission the patient had a cardiopulmonary arrest.	Death due to underlying medical compromise with inability to sustain the stress of large intracerebral hemorrhage. RF SMQ term is a secondary event and did not result directly from medication or treatment method
	IV lorazepam 4mg	78 yo B male. Pertinent medical history of infarct in the right frontal parietal lobe, tardive dyskinesia, dementia, paranoid schizophrenia, post-traumatic stress disorder, congestive heart failure, chronic venous stasis, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, and obesity.	Death due to underlying medical compromise, development of persistent and worsening pneumonia and cardiopulmonary

		Upon arrival to ED seizure continued but successfully treated with lorazepam and phenytoin. Glucose 285mg/dl. On day 2 of hospital admission the patient developed fever and hypoxia (pO2 59mmHg) with hypotension, BP 75/48. Subsequent CXR consistent with aspiration pneumonia. Creatinine 1.5mg/dl with BUN 21 mg/dl. 8 days after admission acute kidney injury considered resolved (creatinine 1.3mg/dl). Patient subsequently had worsening pulmonary status due to pneumonia. The patient died 21 days after admission due to cardio pulmonary arrest.	arrest. RF SMQ term is a secondary event and did not result directly from medication or treatment method
(b) (6)		19 yo B male, no pertinent medical history. Prior to EMS arrival the patient had suicidal ideation, ingested quetiapine. Agonal breathing and grand mal seizure activity are reported. Patient had 4mg IV lorazepam and rescue diazepam prior to ED arrival. Patient not having seizures on ED arrival. After arrival patient had grand mal seizure activity successfully treated but is reported to be pulseless and apneic, then placed on ventilatory. Text consistent with advance cardiac life support procedures. Severe hypoxic encephalopathy reported. Post arrest creatinine 2mg/dl with BUN 17mg/dl. The subject's serum drug screen was positive for tricyclic antidepressants and his seizures and arrest were deemed to be induced by a poisoning of tricyclic antidepressants. Glucose 302mg/dl. 4 days after admission CT scan of head revealed a marked increase in intracranial edema. Herniation seen at the foramen magnum and loss of white matter distinction. Brain death protocol initiated and patient subsequently declared brain dead.	Death due to severe SE, hypoxic encephalopathy and cerebral herniation. RF SMQ term is a secondary event and did not result directly from medication or treatment method

Healthy Volunteers

STUDY 11903, n=36 (single dose, escalation 0.1mg/kg to 0.49mg/kg six steps, 6 patients /group)

The adverse event dataset and serum creatinine results are examined for events that indicate renal dysfunction. There were no events under the SOC "renal and urinary disorders" in the adverse event dataset. There were also no entries for the preferred term "rhabdomyolysis". The clinical chemistry dataset revealed no increase in serum creatinine from screening to day 1 or day 2 post autoinjector dosing in any dose group. Creatinine units were in mg/dl. Only negative changes were identified with maximum of -0.2mg/dl. Mean and median change from screening (baseline) to post injection day 1 and 2 are shown in [Table 37](#).

Table 37 Study 11903 Serum Creatinine Change from Baseline to Post Injection Day 1 and Day 2 (n= 36)

dose group	N in group	mean day 1	mean day 2	median day 1	median day 2
0.10 mg/kg	6	0.0	0.0	0.0	0.0
0.18 mg/kg	6	-0.1	-0.1	-0.1	-0.1
0.25 mg/kg	6	-0.1	-0.1	-0.1	-0.1

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0.33 mg/kg	6	-0.1	-0.1	-0.1	0.0
0.40 mg/kg	6	-0.1	0.0	-0.1	0.0
0.49 mg/kg	6	0.0	0.0	0.0	0.0

Study 1001, n=24 (10mg autoinjector x 2 separated by 1min or 10 min, 2-way, randomized sequence, open-label, crossover with 1 day between periods).

The adverse event data set examination reveals one patient with an entry in the SOC “renal and urinary disorders” of the preferred term “enuresis”. This occurs in the treatment sequence of 1 x 10mg midazolam separated by < 1 minute. There are no SOC “investigations” entries for elevated creatinine. There were no preferred term entries for “rhabdomyolysis” or “Blood creatinine increased”. The screening and post injection serum creatinine values for laboratory dataset (DC-AA.xpt) are examined. The maximum creatinine entry is 1.02mg/dl with no high value flag entries.

Study 1002, n= 24: TRT A-10mg autoinjector x 2 separated by 1min, TRT B- Atropine 2.0 mg auto-injector followed 10 min later by midazolam 2 x 10 mg auto-injectors administered <1 min apart 2-way, randomized sequence, open-label, crossover with 1 day between periods).

The adverse event dataset of treatment A (10mg autoinjector x 2 separated by 1min) is examined. There were no entries for the SOC “renal and urinary disorders” or “investigations”. There were no preferred term entries for “rhabdomyolysis” or “Blood creatinine increased”. The screen and post injection serum creatinine values for laboratory dataset (DC-AA.xpt) are examined. The maximum creatinine entry is 1.15mg/dl with no high value flag entries.

Study 1003, n= 24: TRT A-10mg autoinjector x 2 separated by 1min, TRT B- Atropine (2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL), combined in a single auto-injector followed by midazolam 2 x 10 mg auto-injectors administered <1 min apart, 2-way, randomized sequence, open-label, crossover with 1 day between periods).

The adverse event dataset of all treatment period including (10mg autoinjector x 2 separated by 1min) is examined (no treatment period identifier was present; treatment period variable was populated for all entries with “all”). There were no entries for the SOC “renal and urinary disorders” or “investigations”. There were no preferred term entries for “rhabdomyolysis” or “Blood creatinine increased”.

The screen and post injection serum creatinine values for laboratory dataset (DC-AA.xpt) are examined. The maximum creatinine entry is 1.31 mg/dl. This is from one patient (4.1%) with an out of reference range high flag but “no” as a clinically significant entry. The patient had a screening creatinine value of 1.19 mg/dl (baseline). The baseline to post injection increase is 10.1%. No other out of reference range high values are identified. The next highest of all creatinine entries is the baseline value of the above noted patient 1.19 mg/dl.

Study 1004, n= 24: TRT A-10mg autoinjector x 2 separated by 1min, TRT B- Oral pyridostigmine (30 mg) followed 120 min later by atropine (2.1 mg; 0.7 mL) and 2-PAM (600 mg; 2.0 mL) by auto-injector followed by midazolam 2 x 10 mg auto-injectors administered <1 min apart, 2-way, randomized sequence, open-label, crossover with 1 day between periods).

The adverse event dataset of all treatment period including (10mg autoinjector x 2 separated by 1min) is examined (no treatment period identifier was present; treatment period variable was populated for all entries with “all”). There were 2 entries for the SOC “renal and urinary disorders” with corresponding preferred terms “dysuria” and “hematuria”. The treatment sequence of onset could not be determined in the dataset, however both events are not SAEs. These events are not due to renal dysfunction. There are no preferred term entries for “rhabdomyolysis”, “Blood creatinine increased” or renal failure terms.

Study 1005, n= 250: Study to evaluate safety of IM midazolam autoinjector. 2 x 10 mg auto-injections administered <1 min apart. Single dose study.

The post screen entries of the adverse event dataset are examined. There were no entries for the SOC “renal and urinary disorders” while there were 22 entries for “investigations” and 13 entries for “Musculoskeletal and connective tissue disorders”. The entries for “investigations” and “Musculoskeletal and connective tissue disorders” are examined for preferred terms “rhabdomyolysis” and “Blood creatinine increased”. These terms are not present.

The screen and post injection serum creatinine values for laboratory dataset (DC-AA.xpt) are examined. Two patients (0.8%) are identified with post injection out of reference range high values for serum creatinine. These occur in subjects (b) (6) who both had post injections creatinine values of 1.26 mg/dl. The screening (baseline) values of subjects were 1.13mg/dl and 1.05mg/dl respectively. These creatinine increases represent an 11.5% increase for subject (b) (6) and a 20% increase for subject (b) (6). Blood urea nitrogen and serum potassium values for both subjects are within reference range.

Reviewer Comment: there are no entries in the healthy volunteer (autoinjector) dataset for “rhabdomyolysis” or terms associated with renal failure. One subject in study 1003 had a 10.1% increase in serum creatinine that was sufficient to go out of reference range. In Study 1005 there were two subjects (0.8%) with an elevation of creatinine values to “out of reference range”. These represented an 12% and 20% increase over baseline. These were small incremental elevations in of creatinine over the upper boundary of normal reference range. In the absence of renal dysfunction adverse event terms and absence of alteration in creatinine values after the highest autoinjector dosing that was delivered in study 11903, there is no signal

for adverse renal safety from IM midazolam autoinjector dosing. There is also no signal for rhabdomyolysis.

Renal Failure Overall Summary

In the healthy volunteer studies midazolam was delivered at twice the dose with multiple autoinjector deliveries with no signal for renal dysfunction. This provides evidence that midazolam by autoinjector is not inherently nephrotoxic. The healthy volunteer results indicate there is a property of the intended population, patients in status epilepticus, that results in the observed renal adverse safety events.

Examination of the most frequent preferred terms occurring in the patients with a positive renal failure SMQ compared to those without a renal failure SMQ term reveals preferred terms associated with more serious and challenging medical conditions among the patients with renal failure SMQ terms. From among this cohort there was a higher frequency of “respiratory failure” (5 fold more frequent), “Hypertension” (5.8 fold more frequent), “hypotension” (5 fold more frequent), “Acute Respiratory failure” (4.3 fold more frequent), “anemia” (5.7 fold more frequent”.

Examination of the 108 patients with a renal failure SMQ term in the MRP, ADSEALL dataset (all patients including re-enrollment) reveals an equal distribution of these patients between the IM midazolam and IV lorazepam treatment arms.

There is a higher frequency of rhabdomyolysis among those with a renal failure SMQ term. Further examination of the characteristics of these patients reveals those with rhabdomyolysis in the IM midazolam treatment arm had a longer latency to seizure cessation. This is a reverse of the pattern seen in the remaining patient cohort without a renal failure SMQ term. Although there is a longer latency among the IM midazolam group, there remains a larger proportion of successful treatment outcomes than in the IV lorazepam treatment arm with rhabdomyolysis. This indicates that the occurrence of rhabdomyolysis in IM midazolam use is not a marker for treatment failure.

From among the patients with a renal failure SMQ term there were 10 patients with a fatal outcome. Among the patients with a positive renal failure SMQ term with a fatal outcome 70% were in the IV lorazepam treatment arm and 30% in the IM midazolam treatment arm. Examination of the narrative reports of those with a fatal outcome reveal the renal failure SMQ event was an epiphenomenon of the severe medical illness associated with status epilepticus event, the severity of the status epilepticus event or status epilepticus and a negative synergy with an underlying co-morbidity.

In conclusion, there was no evidence of a selective risk of renal failure SMQ terms in the IM midazolam treatment group. There was an excess of rhabdomyolysis in the IM midazolam compared to the IV lorazepam treatments of 3.9% vs 2.4% respectively. The reason for this inequality is unclear. Due to the double dummy design 99.6% of all enrollees received an IM autoinjector treatment. A longer latency to seizure cessation could allow development of rhabdomyolysis. This circumstance should not be selective for IM midazolam because as shown in , the mean and median latency to seizure cessation for all patients in the IV lorazepam treatment arm was similar to the IM midazolam patients with rhabdomyolysis. The mean for IM midazolam in the circumstance of rhabdomyolysis was 30 seconds longer. Regardless of cause the IM midazolam patients with rhabdomyolysis retained a higher proportion of treatment success than IV lorazepam patients with rhabdomyolysis.

The higher proportion of preferred terms for serious medically destabilizing events among patients with renal failure SMQ indicates these patients have a more serious course of status epileptics or more serious medical comorbidities or both. The occurrence of the renal failure SMQ terms is distributed equally between both treatment arms as a complication of the severe medical challenge of status epilepticus that may also occur in patients with medical comorbidities that increase their vulnerability to renal complication.

8.5.5. Decreased Oxygen Saturation

RAMPART Study

IM Midazolam

The IM treatment arm of the RAMPART AE dataset with duplicate patients is examined for preferred terms that capture respiratory depression under the SOC “Respiratory, thoracic and mediastinal disorders”. There were 33 (7.3%) patient with adverse events under the preferred terms “Acute respiratory failure”, “Apnoea”, “Hypoxia”, “Respiratory arrest”, “Respiratory depression”, “Respiratory distress”, “Respiratory failure”. Twenty-eight (84%) of these 33 events were SAEs. The same analysis is performed excluding patients <18 years of age where there were 31 (8.0%) patients were identified. Twenty-seven (87.1%) of these 33 events were SAEs.

Study 1005

There were 250 subjects enrolled at two study centers, of which 47% were female. Subjects then entered the Treatment Phase of the study on Day 1 and received the following treatment after an overnight fast of at least 8 hours; 2 x 10 mg midazolam auto-injectors (20 mg total)

with injections separated by < 1 minute. The Treatment Phase included assessments of safety at specified times pre- and postdose on an inpatient basis. Vital signs, AE assessments, clinical laboratory assessments, ECGs, and physical examinations were done at specified times.

There were 13 (5.2%) patients with adverse events with preferred term “oxygen saturation decreased”. None were serious adverse events. There were three subjects with 11 instances captured in a specific category of “Respiratory depression”. None of these were entered as serious adverse events. Two of these three subjects also had entries in the AE dataset of “oxygen saturation decreased”. The total unique subjects with entries for “oxygen saturation decreased” and events of “respiratory depression” is 14 unique subjects (5.6%).

8.6. Safety Analyses by Demographic Subgroups

Age ITT population

An overview is provided for adverse events for the subgroups <17 years of age, 17 to 65 years of age, and >65 years of age for the ITT Population; in which 113 (12.7%) subjects were ≤17 years of age, 656 (73.5%) subjects were 17 years to 65 years of age, and 124 (13.9%) subjects were >65 years of age.

The frequency of adverse events was higher in the subgroup of subjects >65 years of age (83 [66.9%] subjects) compared with the subgroups of subjects between the ages of 17 and 65 (321 [48.9%] subjects) and <17 years of age (42 [37.2%] subjects).

The frequency of drug-related adverse events was higher in the subgroup of subjects >65 years of age (34 [27.4%] subjects) compared with the subgroups of subjects between the ages of 17 and 65 (94 [14.3%] subjects) and <17 years of age (18 [15.9%] subjects). These trends were apparent for both treatments.

Overall, a greater percentage of severe, life-threatening, and fatal adverse events were observed in the subgroup >65 years of age compared with the subgroups between 17 to 65 years and <17 years of age.

For subjects <17 years of age, the most frequent adverse events were the following:

- Convulsion: 4 (7.0%) subjects in the IM midazolam group and 6 (10.7%) subjects in the IV lorazepam group;
- Vomiting: 3 (5.3%) subjects in the IM midazolam group and 5 (8.9%) subjects in the IV lorazepam group;

- Respiratory depression: 2 (3.5%) subjects in the IM midazolam group and 5 (8.9%) subjects in the IV lorazepam group;
- Pyrexia: 5 (8.8%) subjects in the IM midazolam group and 2 (3.6%) subjects in the IV lorazepam group; and
- Agitation: 2 (3.5%) subjects in the IM midazolam group and 2 (3.6%) subjects in the IV lorazepam group

For subjects 17 to 65 years of age, the most frequent adverse events were the following:

- Convulsion: 49 (14.6%) subjects in the IM midazolam group and 53 (16.5%) subjects in the IV lorazepam group;
- Respiratory depression: 13 (3.9%) subjects in the IM midazolam group and 17 (5.3%) subjects in the IV lorazepam group; and
- Upper airway obstruction: 16 (4.8%) subjects in the IM midazolam group and 7 (2.2%) subjects in the IV lorazepam group.

For subjects >65 years of age, the most frequent adverse events were the following:

- Convulsion: 9 (16.1%) subjects in the IM midazolam group and 6 (8.8%) subjects in the IV lorazepam group;
- Hypotension: 6 (10.7%) subjects in the IM midazolam group and 6 (8.8%) subjects in the IV lorazepam group;
- Respiratory depression: 4 (7.1%) subjects in the IM midazolam group and 7 (10.3%) subjects in the IV lorazepam group;
- Coma: 5 (8.9%) subjects in the IM midazolam group and 4 (5.9%) subjects in the IV lorazepam group;
- Upper airway obstruction: 4 (7.1%) subjects in the IM midazolam group and 4 (5.9%) subjects in the IV lorazepam group;
- Postictal state: 4 (7.1%) subjects in the IM midazolam group and 4 (5.9%) subjects in the IV lorazepam group;
- Hypokalemia: 3 (5.4%) subjects in the IM midazolam group and 5 (7.4%) subjects in the IV lorazepam group;

In summary, convulsion was experienced in the subgroups of subjects <17 years of age and 17 to 65 years of age by a lower percentage of subjects in the IM midazolam group than in the IV lorazepam group. For subjects <17 years of age, 4 (7.0%) subjects in the IM midazolam group and 6 (10.7%) subjects in the IV lorazepam group experienced convulsion. For subjects 17 to 65 years of age, 49 (14.6%) subjects in the IM midazolam group and 53 (16.5%) subjects in the IV

lorazepam group experienced convulsion. In the subgroup of subjects >65 years of age, convulsion was experienced by a higher percentage of subjects in the IM midazolam group (9 [16.1%] subjects) than in the IV lorazepam group (6 [8.8%] subjects).

In all 3 age subgroups of subjects, respiratory depression was experienced by a lower percentage of subjects in the IM midazolam group than in the IV lorazepam group. In the IM midazolam treatment arm the frequency of this adverse event was similar in the <17 year and 17 to 65 year group but nearly doubled to 7.1% in the 65< age group.

In all 3 age subgroups of subjects, upper airway obstruction was experienced by a higher percentage of subjects in the IM midazolam group than in the IV lorazepam group with the highest frequency in the 65< age group at 7.1%.

In the subgroups of subjects <17 years of age and >65 years of age, pyrexia was experienced by a higher percentage of subjects in the IM midazolam group than in the IV lorazepam group.

In the subgroup of subjects 17 to 65 years of age, hypotension was experienced by a lower percentage of subjects in the IM midazolam group (6 [1.8%] subjects) than in the IV lorazepam group (12 [3.7%] subjects). In the subgroup of subjects >65 years of age, hypotension was experienced by a higher percentage of subjects in the IM midazolam group (6 [10.7%] subjects) than in the IV lorazepam group (6 [8.8%] subjects). In the subgroup of subjects <17 years of age, 0 (0.0%) subjects experienced hypotension in either treatment group.

Reviewer Comment: there was a higher frequency of event terms associated with more severe course of medical illness in the >65 age group, these included “respiratory depression” and “hypotension” where the frequency was less in the IM midazolam arm than in the IV lorazepam arm. The term coma was more frequent in the >65 age group but with a higher frequency in the IM midazolam arm. The trend of more severe adverse event terms in the older age group is expected due to a higher likelihood of co-morbidities and less reserve to tolerate the extreme physiologic challenge of status epilepticus. Overall, there is not trend for difference in the adverse effects between the <17 and 17 to 65 age groups and generally, as in the total group adverse events, a more favorable profile of adverse events in the IM lorazepam treatment arm.

Sex ITT

In the ITT Population, 488 (54.6%) subjects were male and 405 (45.4%) subjects were female.

The frequency of adverse events was similar in the subgroup of male subjects (252 [51.6%] subjects) compared with the subgroup of female subjects (194 [47.9%] subjects).

There were no apparent gender-related trends in the maximum severity of adverse events.

In males and females, respiratory depression was experienced by a lower percentage of

subjects in the IM midazolam group than in the IV lorazepam group. For males, 13 (5.2%) subjects in the IM midazolam group and 19 (8.0%) subjects in the IV lorazepam group experienced respiratory depression. For females, 6 (3.0%) subjects in the IM midazolam group and 10 (4.8%) subjects in the IV lorazepam group experienced respiratory depression. The findings for this important event term reflect the frequencies seen in the overall treatment arms with no notable trend by sex.

There were no other obvious gender-related trends in the types of adverse events observed across the gender categories for either treatment group and no apparent trends in adverse events across the gender subgroups related to the different treatments (IM midazolam versus IV lorazepam).

Race ITT

Adverse events by race (Black/African American, White, Other) for the ITT Population; in which 453 (50.7%) subjects were Black/African American, 348 (39.0%) subjects were White, and the races included in the Other category were each <5%.

The frequency of adverse events was similar in the subgroup of Black/African American subjects (226 [49.9%] subjects) compared with the subgroup of White subjects (176 [50.6%] subjects) and the subgroup of Other races (44 [47.8%] subjects).

There were no other obvious race-related trends in the types of adverse events observed across the race subgroups for either treatment group and no apparent trends in adverse events across the race subgroups related to the different treatments (IM midazolam versus IV lorazepam).

8.7. Specific Safety Studies/Clinical Trials

none performed

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Data reliant on the listed drug

8.8.2. Human Reproduction and Pregnancy

Data reliant on listed drug

8.8.3. Pediatrics and Assessment of Effects on Growth

Safety data reliant on listed drug. Post marketing requirements are not planned. This product

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has orphan status so PREA is not triggered.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data reliant on the listed drug

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

well established safety issues are present in the listed drug label.

8.9.2. Expectations on Safety in the Postmarket Setting

Post marketing safety is expected to be in alignment with the established use of benzodiazepines in early phase status epilepticus treatment

8.9.3. Additional Safety Issues from Other Disciplines

none identified

8.10. Integrated Assessment of Safety

Introduction

Assessment of the safety dataset is performed by examination of the RAMPART and MRP safety datasets. The RAMPART ITT safety dataset addresses the set of adverse events closest to the administration of the study drug, while in transport to the emergency department and shortly after arrival in patients who represent the study endpoint population, the 1st enrollment patients. This group reflects the more immediate effects of treatment on the episode of status epilepticus.

The next body of adverse events examined is the MRP adverse event dataset. This dataset captures the more complete medical chart data of the RAMPART study patients at the emergency department and safety data from the medical records of patients admitted to the hospital following arrival at the emergency department but after the endpoint of emergency department adjudication of seizure termination. When reviewing this safety dataset, the total population was examined to capture events that occurred to any patient following any enrollment. This approach offers a more comprehensive view of the safety information that is accrued from all treatment courses of status epilepticus.

Integrated Assessment of safety

Deaths

There was an excess of deaths in the IM midazolam arm over the IV lorazepam arm with 13 (59% of deaths) in the IM midazolam arm and 9 (41% of deaths) in the IV lorazepam arm. The imbalance reflects the unequal distribution of serious co-morbidities that increase vulnerability to poor outcome and the variation in the severity of status epilepticus. The death rate in both treatment arms, IM midazolam 2.5%, IV lorazepam 1.8% is notably lower than the literature-based reports where a fatal outcome in status epilepticus occurs in 20% of patients.

SAE

RAMPART

An imbalance in the frequent SAE preferred term “upper airway obstruction” had a noted excess in the IM midazolam treatment arm. No clear reason could be identified. The other medically threatening and serious adverse event terms with high frequency, “convulsion” (which may reflect effectiveness) “Respiratory depression”, “coma”, and “respiratory failure” had a higher frequency in the IV lorazepam arm. As a serious adverse event related to the safety event of special interest, renal failure the frequency of the term “rhabdomyolysis” occurred with equal frequency in both treatment arms.

MRP

The most frequency serious adverse events are consistent with the severity of the underlying illness. These events include epilepsy related terms “convulsion”, “seizure”, and “status epilepticus”. The frequency of all three are higher in the IV lorazepam treatment arm. There is also a high frequency of terms related to respiratory compromise. These terms include “upper airway obstruction”, “respiratory depression”, “respiratory failure”, “acute respiratory failure” and “respiratory distress”. The frequency for all of these terms except “upper airway obstruction” is greater in the IV lorazepam treatment arm. The adverse reaction frequency for epilepsy and respiratory related SAEs is lower in the IM midazolam treatment arm.

Study 1005 (Healthy volunteers)

There was a single serious adverse event in study 1005. This subject had an adverse event preferred term of “thrombocytopenia”. Causality is confounded by treatment with depot injection of medroxyprogesterone acetate (Depo-provera). The patient had a subsequent diagnosis of ITP

TEAE

RAMPART

In the ITT population there was a higher frequency of any adverse event in the IV lorazepam group than in the IM midazolam treatment arm, 233 (52.4%) and 213 (47.5%) respectively. There were 20 preferred terms with a frequency >1%. Terms with a higher frequency in the IM midazolam treatment arm were; Upper airway obstruction, Agitation, Pyrexia, Mental status changes, Postictal state, Renal failure acute, Metabolic acidosis, Hypomagnesaemia, Leukocytosis. From among these terms with frequency higher in the IM midazolam treatment arm the highest frequencies, 9 or more patients, were in the terms; upper airway obstruction, agitation, pyrexia, mental status changes, post ictal state and renal failure acute. The gradient of difference was greatest for the terms; upper airway obstruction and renal failure acute.

The basis of the separation of those terms noted above from the IV lorazepam arm is uncertain. The issue of renal failure is addressed in Submission specific safety issues. No clear cause was identified and a small inequality in the distribution of patient underlying medical condition or severity of status epilepticus episode may explain this different. There were terms of note where the IV lorazepam arm had a higher frequency of occurrence, these include; respiratory depression, hypotension and respiratory failure. These terms may be related to a more severe medical course. The frequency of the term rhabdomyolysis was equal between treatment arms.

MRP

From the TEAE safety event term analysis there were 9 terms of increased interest identified. These terms were “seizure”, “status epilepticus”, “respiratory failure”, “acute kidney injury”, “acute respiratory failure”, “pneumonia”, “rhabdomyolysis”, “thrombocytopenia”, and “torsade de pointes”. These terms are of interest due to the potential relationship to efficacy for example the seizure related terms and the remaining terms due to potential significant safety events related to IM midazolam treatment, see [Table 20](#). Examination of these results reveals two terms of special interest with a higher frequency in the IM midazolam arm than in the IV lorazepam arm. These events are “rhabdomyolysis” where the frequency in the IM midazolam arm is 1.6 x higher than the IV lorazepam and “torsade de pointes”. The case of “torsade de pointes” in patient ^{(b) (6)} is adjudicated later in the review discussion but is found to be due to underlying cardiac disease exacerbated by the severe medical stress of SE and hypoglycemia. The remaining event terms that are associated with severe medical complications of SE, including “acute kidney injury” are more frequent in the IV lorazepam treatment arm.

Study 1005

Treatment emergent adverse events (TEAE) are examined in study 1005. Two events are predominant. These are the preferred terms “somnolence” and “injection site pain” with

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frequencies of 99.6 and 90.4 percent of subjects. There were no events consistent with a new safety signal for IM midazolam.

TEAE Section Summary

There is no clear difference in safety events between the two treatment arms. Overall inequalities are likely due to the severity of the status epilepticus episodes and distribution of the demographics of serious co-morbidities but unrelated to treatment arm.

Submission Specific Safety Issues.

Covered in this discussion are the individual evaluations on respiratory or ventilatory compromise, acute kidney failure and thrombocytopenia.

Thrombocytopenia

Thrombocytopenia will be considered first. A separate evaluation for this event term was initiated late in review after a report was identified in a healthy volunteer after a single dose (2 x 10 mg midazolam autoinjector)

The adverse event preferred term “thrombocytopenia” is examined separately after a single healthy volunteer in study 1005 was found to have a serious adverse event of thrombocytopenia. Examination of the MRP ADSE dataset. Examination of this dataset will capture any occurrence of “thrombocytopenia” from RAMPART adverse event dataset or the MRP medical chart data extraction from the 1023 patient enrollments. This examination identified 35 patients with a “thrombocytopenia” preferred term entry. These events had a frequency of 3.1% in the IM midazolam treatment arm and 3.7% of the IV lorazepam treatment arm. One event in the IV lorazepam arm was entered as an SAE. This patient had concurrent sepsis and systemic inflammatory response syndrome. The unequal distribution of these events with a greater proportion in the IV lorazepam treatment and the single SAE occurrence in the IV lorazepam arm does not support causal relationship, or a notable signal for thrombocytopenia due to IM midazolam.

Respiratory Compromise

Respiratory failure is a complication in one third of status epilepticus episodes.²¹ Examination of adverse events associated with ventilatory compromise / respiratory failure in the RAMPART

²¹ Hawkes MA, Hocker SE. Systemic Complications Following Status Epilepticus. Current Neurology and Neuroscience Reports 2018;18.3. Ibid.3. Ibid.3. Hawkes MA, Hocker SE. Systemic Complications Following Status Epilepticus. Current Neurology and Neuroscience Reports 2018;18.3. Hawkes MA, Hocker SE. Systemic

study and MRP revealed a higher frequency of respiratory compromise events in the IV lorazepam treatment arm. The maximum frequency of total respiratory compromise events of all preferred term in the IV lorazepam and IM midazolam treatment arms were 26.3% and 23.5% respectively. These do not exceed the frequency of 33% of status epilepticus events reported in the medical literature. Review of the adverse events in the PK and safety study of healthy volunteers who received twice the dose (20mg) of midazolam as patients in the RAMPART study did not identify any events that required measures of advance life support such as positive pressure ventilation of any means either with a bag valve mask apparatus or mechanical ventilation. This difference between healthy volunteers and status epilepticus patients is evidence that the primary driver of ventilatory compromise / respiratory failure in the status epilepticus cohort is the sustained seizure more than adverse benzodiazepine drug effect. The IV lorazepam had a higher frequency of overall respiratory events than the IM midazolam by a small margin. This provides assurance there is no unexpected mechanism to cause respiratory compromise with the use of IM midazolam.

Renal Failure

There was no evidence of a selective risk of renal failure SMQ terms in the IM midazolam treatment group. There was an excess of rhabdomyolysis in the IM midazolam compared to the IV lorazepam treatments of 3.9% vs 2.4% respectively. The reason for this inequality is unclear. Due to the double-dummy design 99.6% of all enrollees received an IM autoinjector treatment. A longer latency to seizure cessation could allow development of rhabdomyolysis. This circumstance should not be selective for IM midazolam because as shown in , the mean and median latency to seizure cessation for all patients in the IV lorazepam treatment arm was similar to the IM midazolam patients with rhabdomyolysis. The mean for IM midazolam in the circumstance of rhabdomyolysis was 30 seconds longer. Regardless of cause, the IM midazolam patients with rhabdomyolysis retained a higher proportion of treatment success than IV lorazepam patients with rhabdomyolysis.

The higher proportion of preferred terms for serious medically destabilizing events among patients with renal failure SMQ indicates these patients have a more serious course of status epilepticus or more serious medical comorbidities or both. The occurrence of the renal failure SMQ terms is distributed equally between both treatment arms as a complication of the severe medical challenge of status epilepticus that may also occur in patients with medical comorbidities that increase their vulnerability to renal complications.

Conclusion

Complications Following Status Epilepticus. Current Neurology and Neuroscience Reports 2018;18.3. Hawkes MA, Hocker SE. Systemic Complications Following Status Epilepticus. Current Neurology and Neuroscience Reports 2018;18.

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Overall, no signal specific to IM midazolam emerged in review. Extensive examination of potential respiratory compromise and renal failure in section 8.5 did not identify a clear safety signal. Where there was separation between treatment arms with an excess in IM midazolam the difference is likely due to random inequality in the co-morbidities or the severity of the status epilepticus episode that are not unexpected in when this severe medical event occurs. There was separation between the treatment arms with an excess in the IV lorazepam arm of specific terms that was not unexpected. These are the respiratory compromise terms. The rapid rise to lorazepam C_{max} may be expected in some compromised (by the underlying illness) patients to cause depressed ventilatory function.

9. Advisory Committee Meeting and Other External Consultations

none planned

10. Labeling Recommendations

10.1. Prescription Drug Labeling

10.2. Nonprescription Drug Labeling[
N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

None Planned

12. Postmarketing Requirements and Commitments

13. Appendices

13.1. References

See footnotes

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): RAMPART

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>262</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Preferred Terms in the Acute Central Respiratory Depression MMQ-SMQ (Broad Search) MedDRA v16.0

Acute respiratory failure	Cardiopulmonary failure	Neonatal anoxia
Alveolar oxygen partial pressure abnormal	Central-alveolar hypoventilation	Neonatal asphyxia
Alveolar oxygen partial pressure decreased	Cheyne-Stokes respiration	Neonatal hypoxia
Anoxia	Continuous positive airway pressure	Neonatal respiratory acidosis
Apnea	Cyanosis	Neonatal respiratory arrest
Apnea neonatal	Cyanosis central	Neonatal respiratory depression
Apnea test abnormal	Death neonatal	Neonatal respiratory distress
Apneic attack	Dependence on respirator	Neonatal respiratory distress syndrome prophylaxis
Asphyxia	Dyspnea	Neonatal respiratory failure
Bilevel positive airway pressure	Endotracheal intubation [1]	Oxygen saturation abnormal
Blood gases abnormal	End-tidal CO2 abnormal	Oxygen saturation decreased
Blood pH abnormal	End-tidal CO2 decreased	Oxygen saturation immeasurable
Blood pH decreased	Hyperbaric oxygen therapy	Oxygen supplementation
Bradypnea	Hypercapnia	PaO2/FiO2 ratio decreased
Breath holding	Hypercapnic coma	PCO2 abnormal
Breath sounds abnormal	Hypopnea	PCO2 increased
Breath sounds absent	Hypoventilation	PO2 abnormal
Capnogram abnormal	Hypoventilation neonatal	PO2 decreased
Carbon dioxide abnormal	Hypoxia	Positive end-expiratory pressure
Carbon dioxide increased	Intermittent positive pressure breathing	Postoperative respiratory failure
Cardiac arrest	Irregular breathing	Respiration abnormal
Cardiac arrest neonatal	Life support	
Cardio-respiratory arrest	Lung hypoinflation	
Cardio-respiratory arrest neonatal	Mechanical ventilation	
Cardio-respiratory distress	Mechanical ventilation complication	

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Respiratory acidosis	Respiratory gas exchange	decreased
Respiratory arrest	disorder	Venous oxygen saturation
Respiratory depression	Respiratory paralysis	abnormal
Respiratory depth	Respiratory rate decreased	Venous oxygen saturation
decreased	Respiratory therapy	decreased
Respiratory disorder	Sleep apnea syndrome	Ventilation perfusion
Respiratory disorder	Upper airway obstruction	mismatch
neonatal	[1]	Ventilation/perfusion scan
Respiratory distress	Venous oxygen partial	abnormal
Respiratory failure	pressure	Wean from ventilator
Respiratory fume	abnormal	Weaning failure
inhalation	Venous oxygen partial	
disorder	pressure	

13.4. Acute Renal Failure SMQ (Broad Search) MedDRA v16.0

Acute phosphate nephropathy	Hypercreatinemia
Acute prerenal failure	Neonatal anuria
Albuminuria	Nephropathy toxic
Anuria	Nephritis
Azotaemia	Oedema due to renal disease
Blood creatinine abnormal	Oliguria peritoneal dialysis
Blood creatinine increased	Prerenal failure
Blood urea abnormal	Protein urine present
Blood urea increased	Proteinuria
Blood urea nitrogen/creatinine ratio	Renal failure
increased	Renal failure acute
Continuous haemodiafiltration	Renal failure neonatal
Creatinine renal clearance abnormal	Renal impairment
Creatinine renal clearance decreased	Renal impairment neonatal
Creatinine urine abnormal	Renal function test abnormal
Creatinine urine decreased	Renal transplant
Crystal nephropathy	Renal tubular disorder
Dialysis	Renal tubular necrosis
Glomerular filtration rate abnormal	Tubulointerstitial nephritis
Glomerular filtration rate decreased	Urea renal clearance decreased
Haemodialysis	Urine output decreased

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/s/

STEVEN T DINSMORE
09/13/2018

PHILIP H SHERIDAN
09/13/2018