CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216359Orig1s000

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA	216359
SD#	1
Sequence Number	0001
Sponsor	Rafa Laboratories
Drug	Midazolam
Proposed Indication	Treatment of status epilepticus in adults
Material Submitted	Original NDA
Date Received	3/28/22
Date Review Completed	7/22/22
Reviewer	Steven Dinsmore, DO

1. Introduction

The applicant has submitted an original NDA for Midazolam Injection, Autoinjector (AI) for intramuscular (IM) , NDA 216359. The application is being submitted as a 505(b)(2) marketing application. The basis for NDA 216359 is the listed drug (LD) Seizalam (midazolam injection) by Meridian Medical Technologies, Inc which was approved under NDA 209566 on September 14, 2018. Midazolam Injection (Autoinjector) and Seizalam share the same active ingredient, dosage form, route of administration, recommended dose, and indication; however, the Midazolam Injection AI formulation does not contain the same active and inactive ingredients in the same concentrations. Midazolam Injection is more concentrated with 14.3 mg/ml (10 mg/0.7 mL) midazolam compared with 5 mg/mL (50 mg/10 mL) in Seizalam.

No clinical trials were conducted to prove efficacy. On May 19, 2020, the Type B Pre-NDA meeting minutes confirmed that, if bioequivalence could be established between Midazolam Injection AI and Seizalam, results from the Phase 1 study (RLM-559-01) could support reliance upon the Agency's previous finding of the safety and effectiveness of Seizalam. The results of a Phase 1 pharmacokinetic (PK)/relative bioavailability study (RLM-559-01) conducted by the applicant has provided an adequate scientific bridge for this application to rely on the relevant labeling information of the LD.

2. Study RLM-559-01 Clinical Study / Bridging Study

One pivotal study RLM-559-01 was submitted as a bridging study to support the 505(b)(2) regulatory pathway utilizing Seizalam (NDA 209566) as the LD with establishment of bioequivalence to the test product Midazolam Injection AI, NDA 216359.

Ethical Content of The Study

The Applicant has submitted a signed Form 3454 with the attestation "I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests" and inclusion of the list of all investigators. In

Section 5.2 (Ethical Content of the Study) the Study RLM-559-01 CSR attests that the study was conducted in accordance with GCP.

Study Design

This Phase 1, open-label, crossover, comparison study was designed to evaluate the safety and PK characteristics of a single 10 mg IM dose of Midazolam Injection via the test product autoinjector (Treatment A) compared to a single 10 mg IM dose of Midazolam via the marketed LD Seizalam vial and syringe injection (Treatment B) in healthy male or female adult subjects. The study period was defined as the 29-day period that included a clinic visit for injection at Day 1, an additional clinic visit for injection at Day 15, and an end of study visit at Day 29. The study period ended after the Day 29 visit. Figure 1 is a study schematic diagram.

Primary Objectives:

To assess the relative bioavailability between test product (Midazolam Injection AI) and reference product (midazolam via needle and vial) and to monitor the safety of test product and reference product in healthy adult human subjects.

Methodology:

This was a Phase 1, open-label, crossover, comparison study to evaluate the safety and PK characteristics of a single IM dose of 10 mg Midazolam Injection AI compared with marketed LD Seizalam (Midazolam Injection, syringe and vial).

Number of Subjects (Planned and Analyzed):

Forty subjects were enrolled into the study.

There were 36 subjects analyzed in this population set. A total of 4 subjects were excluded from the PK population: 3 subjects were excluded due to completing treatment Period 1 only, and 1 additional subject was excluded due to having no quantifiable concentrations of Midazolam or 1'-hydroxymidazolam following treatment Period 1. An investigation from the site was performed to explore the cause of no quantifiable drug in system in this one subject, suggesting that there was an error in administration of the auto-injector by study staff although the root cause was not determined, see Appendix.

Treatments:

Midazolam Injection (10 mg) was administered in one single dose using either Rafa's Autoinjector (n = 20) or the marketed (Seizalam) Midazolam (vial with a 22-gauge, ¾ inch needle) (n = 20) into the anterolateral thigh muscle in Period 1. Subjects who were administered Midazolam Injection AI in Period 1 received the marketed Midazolam Vial in

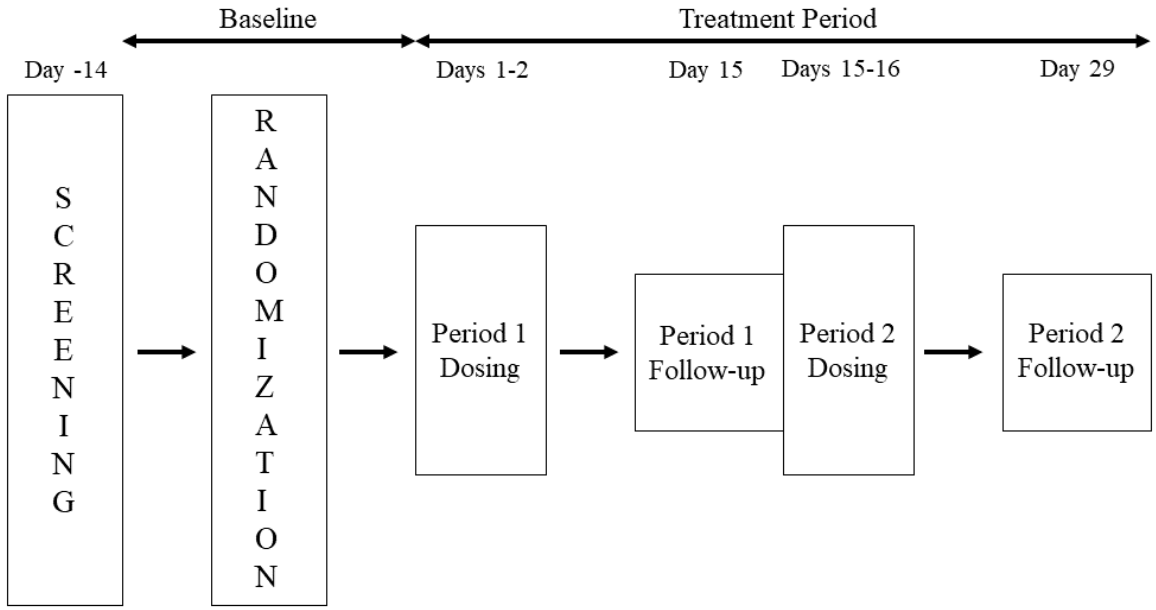
Period 2, and subjects who received the marketed Midazolam Vial in Period 1 received Midazolam Injection AI in Period 2,

Treatment A: (Test) Rafa Laboratories' Midazolam Injection AI, 10 mg is a sterile solution for intramuscular injection. The dose administered was 10 mg in 0.7 ml. All Midazolam Injection AI 10 mg administrations were from Batch number 701597.

Treatment B: (Reference) Seizalam Midazolam vial is supplied as a 50 mg/10 mL sterile solution. The dose administered was 10 mg in 2 mL. All Seizalam Midazolam vial administrations were from Lot #90-283-DK.

There was a washout period of 14 days between each drug administration.

Figure 1 Study RLM-559-01 Schematic



PK Sampling:
Blood samples were collected at pre-dose (1-2 hours) and at 3±1, 6±1, 10±1, 15±1, 20±2, 30±2, 45±2 minutes post-dose, and 1±5, 2±5, 3±5, 4±5, 6±5, 8±5, 12±10, 24±10, and 30 hours ±10 minutes post-dose.

Criteria for PK Comparison:
The following PK parameters were calculated for Midazolam using standard non-compartmental methods: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, K_e, $t_{1/2,}$ CL and Vz. The following standards for relative bioavailability were applied for Midazolam: 90% confidence interval of

the geometric least square mean ratio of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ of the test and reference products for Midazolam are completely contained in the range of 80.00 to 125.00 % (limits inclusive) for ln-transformed data.

Results:
Overall, 39 of 40 enrolled subjects received Midazolam using the autoinjector and 38 of 40 enrolled subjects received Midazolam using the marketed vials.

Data of 36 subjects for pharmacokinetic analysis and statistical analysis were used. The descriptive statistics for PK parameters of each treatment are shown in Table 1. Table 2 summarized the ratio of PK parameters and confidence intervals (C.I.). ***The OCP reviewer conducted independent analysis and verified the PK results concluding that the Cmax AUC0-last and AUC0-inf were within the acceptable limits of 80.00% to 125.00%.***

Table 1 Summary of Key Pharmacokinetic Parameters for Midazolam by treatment

Treatment/ Number of subjects	**$AUC_{0\text{-}last}$ (ng.h /mL)**	**$AUC_{0\text{-}\infty}$ (ng.h /mL)**	**Cmax (ng/mL)**	**$t_{1/2}$ (h)**	**t_{max} (h)**
A (Autoinjector, n=36)	444±127	454±134	127±47.3	5.16± 1.77	NC
B (Marketed Vials, n=36)	419±105	428±111	123±45.7	4.75±1.65	NC

Source: Clinical Study Report (body 4); Study Number: rlm-559-01, Table 5-4, Page 29 of 260.

Table 2 Relative Bioavailability ANOVA for Midazolam after a Single Intramuscular Injection of 10 mg Midazolam Administered via Rafa's Midazolam Autoinjector versus 10mg Seizalam Vial & Syringe, Ratio of the Least squares Geometric Means (LSM) of PK parameters and 90% Confidence Intervals

Parameter	**Units**	**Test N (Trt A)**	**Reference N (Trt B)**	**Geometric LSM (Test)**	**Geometric LSM (Reference)**	**Geometric LSM Ratio (%)**	**90% Confidence Interval**
AUC_{inf}	h*ng/mL	36	36	437	414	105.56	(100.96, 110.17)
AUC_{last}	h*ng/mL	36	36	428	407	105.16	(100.67, 109.98)
C_{max}	ng/mL	36	36	119	114	104.39	(90.45, 120.28)

3. Safety

SAE and TEAE Leading to Study Medication discontinuation

Within the safety population, 1 subject out of 39 (2.6%) who was administered Midazolam Injection AI experienced an SAE leading to withdrawal. The subject (subject [redacted]) experienced syncope which was considered by the investigator to be not related to either the drug or the device. No SAEs were observed in the 38 subjects who were administered the marketed vials of Midazolam.

Subject [redacted] Narrative Summary

Subject [redacted] is a [redacted] with a medical history relevant for stable sinus bradycardia. On [redacted] at approximately [redacted] (approximately 32.5 hours following Midazolam injection via the auto-injector), the subject was at home eating dinner with friends when [redacted] began to look and feel unwell. [redacted] then experienced an episode of syncope with witnessed tonic-clonic movements for approximately 2 - 3 minutes in length. [redacted] was transported to the local emergency department (ED) by Emergency Medical Service.

While in the ED, a central nervous system (CNS) workup was performed and a computerized tomogram (CT) scan was obtained, all of which were unremarkable. Laboratory investigations were remarkable for chloride of 108 mmol/L (reference range 98 - 107 mmol/L), AST 36 U/L (reference range <34 U/L), alkaline phosphatase 42 U/L (reference range 46-116 U/L), and urinalysis specific gravity of 1.003 (reference range 1.005 - 1.030).

The subject recovered from the serious event of syncope/convulsions on [redacted] and was discharged from the ED after an observation period of 13 hours. [redacted] was also scheduled for an outpatient neurological follow-up.

On [redacted], the subject contacted the reporting clinical site with a request to withdraw from Period 2 of the study (scheduled to receive Midazolam administration via marketed vials) secondary to the syncopal convulsions [redacted] experienced post study drug administration and clinic discharge. [redacted] reported feeling much better at that time and confirmed that [redacted] had not had a reoccurring or sequelae event. The reporting clinical site made contact with the subject again on the following 2 days with no reported reoccurrences.

Reviewer Comment: The event of syncope that occurred 3.7 x $t_{1/2}$ (given the maximum reported $t_{1/2}$) and 5.8 x $t_{1/2}$ based on the mean $t_{1/2}$ following midazolam administration (see Table 1). Therefore, the syncopal episode did not have a clear temporal relationship to test product treatment. The event had clinical characteristics of a syncope of hemodynamic origin with associated epileptiform movements “syncopal seizure”. There is a remote possibility that this was a withdrawal seizure following the single midazolam dose.

Treatment Emergent Adverse Events (TEAE)

TEAE that occurred following the single dose of Midazolam Injection AI are compared to events that occurred following the single dose of Midazolam via needle from vial, see Table 3. This analysis reveals there was overlap for only one preferred term from among the two differing

treatment administrations. This preferred term was "injection site pain" where 3 (15%) subjects in the Autoinjector administration period and 1 (5%) subject in the needle from vial administration period experience injection site pain. From among the remaining 20 preferred terms occurring in the Study RLM-559-01 ADAE (xpt adverse events) dataset there were none in common between the autoinjector treatment period and the needle from vial treatment period.

The next TEAE with a frequency greater than a single occurrence, after "injection site pain", in the Midazolam Injection AI treatment period were "systolic hypertension", "hypertension" and "anaemia" that each occurred in 2 (10%) subjects. The events of "systolic hypertension" and "hypertension" are plausibly associated with local injection site pain at the time of midazolam administration via autoinjector. The 2 events of "anaemia" were explored further and reveal that in the first (subject (b) (6)) of the two subjects a single outlier that was an Out of Reference Range (OORR) low hemoglobin occurred 7 hours after a pre-treatment normal value and in the second subject (subject (b) (6)) the pre-treatment value was an OORR low at 11.6g/dL with improvement at the 7hr post-dose value, see Figure 2, Figure 3 and Table 5. None of these events were reported as an SAE or resulted in study discontinuation. The remaining TEAE that occurred in association with Midazolam Injection AI were "Syncope", "Muscular weakness", "Gamma-glutamyltransferase increased", "Diarrhoea", "contusion" and "Blood urine present" that occurred in one subject each.

Figure 2 Subject (b) (6) Hb by Study Time Marker, Vial-Needle and Midazolam Injection AI

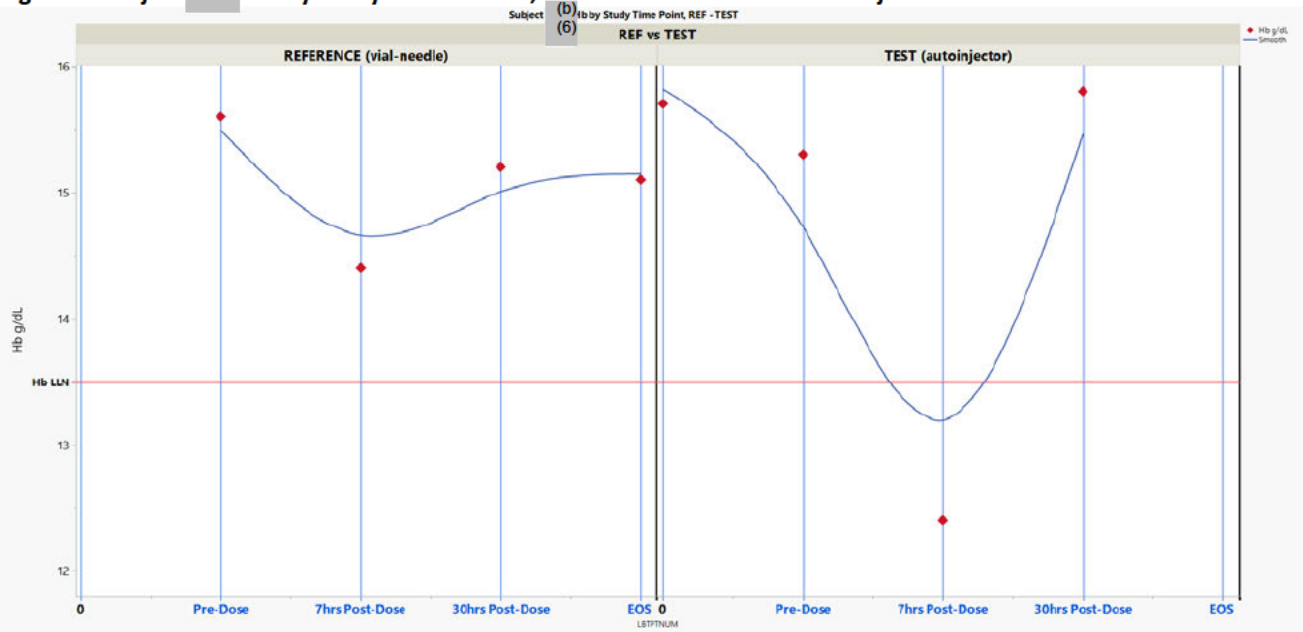
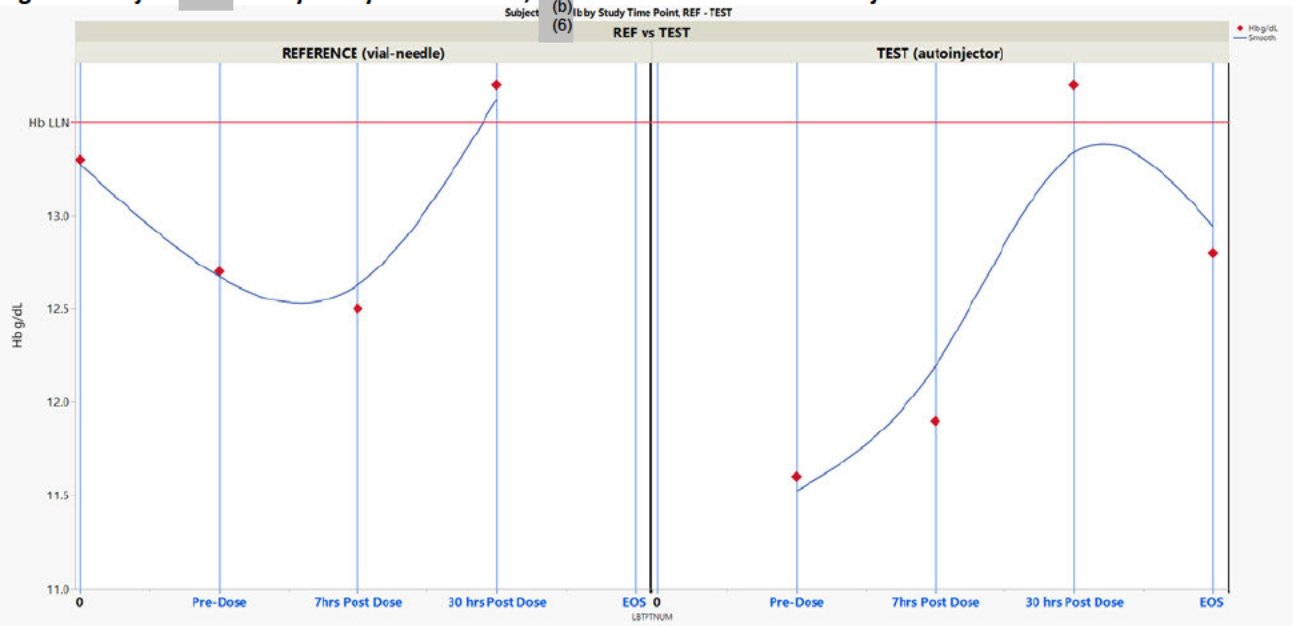


Figure 3 Subject (b) (6) Hb by Study Time Marker, Vial-Needle and Midazolam Injection AI



The single event of "Syncope" occurred in subject (b) (6) discussed in the previous section. The event of "Muscular weakness" had a verbatim term entry of "Left lower extremity weakness" and may be related to injection site pain. The remaining 4 events do not have a clear mechanistic relationship to the Midazolam Injection AI administration.

There most frequent events with greater than one occurrence following "Injection site pain" in the needle from vial treatment were "Dizziness" and "Tachycardia" that each occurred in 2 (10%) subjects. These events are plausibly associated with local injection site pain at the time of midazolam injection via needle from vial administration. Alternatively, dizziness may be a direct effect of midazolam. None of these events were reported as an SAE or resulted in study discontinuation. The remaining TEAE that occurred in association with midazolam administered via needed and vial were "Aspartate aminotransferase increased", "Blood calcium decreased", "Blood potassium decreased", "Flushing, "Hepatic enzyme increased", "Hypotension", "Nausea", "Vomiting" that occurred in one subject each. These events do not inform the safety of the autoinjector deliver of midazolam except as comparators for frequencies of AEs.

Table 3 TEAE Frequencies Observed with Midazolam Injection AI and needle from vial administration.

Preferred Term	# Pts of Midazolam Injection AI	% Pts of Midazolam Injection AI	# Pts of Vial-Needle	% Pts of Vial-Needle
Injection site pain	3	15	1	5
Systolic hypertension	2	10	0	0
Hypertension	2	10	0	0
Anaemia	2	10	1	5
Syncope	1	5	0	0
Muscular weakness	1	5	0	0

Preferred Term	# Pts of Midazolam Injection AI	% Pts of Midazolam Injection AI	# Pts of Vial-Needle	% Pts of Vial-Needle
Gamma-glutamyltransferase increased	1	5	0	0
Diarrhoea	1	5	0	0
Contusion	1	5	0	0
Blood urine present	1	5	0	0
Dizziness	0	0	2	10
Tachycardia	0	0	2	10
Aspartate aminotransferase increased	0	0	1	5
Blood calcium decreased	0	0	1	5
Blood potassium decreased	0	0	1	5
Flushing	0	0	1	5
Hepatic enzyme increased	0	0	1	5
Hypotension	0	0	1	5
Nausea	0	0	1	5
Otitis externa	0	0	1	5
Vomiting	0	0	1	5

Reviewer Comment: The single SAE that occurred associated with Midazolam Injection AI was syncope without temporal relationship to treatment. The most predominant TEAE that occurred with autoinjector treatment were likely secondary to injection site pain while the remaining events were not causally related to Midazolam Injection AI. There is no safety signal that represents a significant new risk of midazolam using the autoinjector product compared to the needle from vial administration.

Laboratory Studies

Samples for clinical chemistry and hematology laboratory studies were collected 1-2 hours pre-dose and at 7 hours, 30 hours, and 14 days post-Midazolam administration in both treatment periods 1 and 2. This sampling schedule captures clinical laboratory samples for both midazolam administration via autoinjector (test product-Midazolam Injection AI) and from the midazolam via needle from vial administration (reference product,). The subsequent discussion is focused on laboratory results that are related to the Midazolam Injection AI treatment unless a comparison to the corresponding needle from vial treatment would be further informative.
Approach to Clinical Laboratory Analysis

Examination of the Applicant's presentation of laboratory results from shift tables (summary of results assessed as normal, abnormal, not clinically significant (NCS) and abnormal, clinically significant (CS) as well as individual outliers) was performed. The reviewer also performed an independent assessment of clinical chemistry and hematology results with the following two conditions: entries identified by the Applicant's variable "CLINSIG" with a value of "Abnormal, NCS" and a post treatment result that had a greater than or less than 25% change from the baseline (pre-treatment) value were evaluated. Stated alternatively, if the post treatment result was identified as "Abnormal, NCS" and was within 25% (inclusive) in either the negative or positive direction from the baseline value, the result was not further examined. Laboratory

values identified by the "CLINSIG" variable as normal were not evaluated further. This screening method was chosen to assess if the Applicant designation of "Abnormal, NCS" contained laboratory values with large excursions from baseline that but remained close to reference range boundaries. Such changes could identify a safety signal even if the divergence from reference range did not, if taken in isolation, appear clinically significant.

The 25% boundary method reveals there were a total of 353 entries identified by the Applicant as abnormal but not clinically significant. From among these the reviewer's method identified 73 that had a result that was divergent from baseline value by more than 25% while 280 entries had results within the limits of 25% change from baseline, exactly equal to 25% from baseline or without calculable change from baseline, see Table 4. Those entries with a greater than 25% increase or decline from baseline were subject to further assessment for clinical significance in the following sections.

Table 4 Distribution of Applicant "CLINSIG" and Reviewer "+/-, >25% CHG" Assignments for Chemistry and Hematology Laboratory Results.

Greater than or less than 25% change from baseline = 1	Direction of Change from Baseline >25% +/- with Polarity (1=, >25), (0=, <25)	CLINSIG value	# of Clinical Chemistry or Hematology entries
1	0	Abnormal, not clinically significant	58
1	0	Normal	239
1	1	Abnormal, not clinically significant	15
1	1	Normal	288
Within the 25% change from baseline boundaries		Abnormal, clinically significant	4
		Abnormal, not clinically significant	243
		Normal	2457
% Change exactly equal to 25% from Baseline		Normal	7
Unable to calculate percent change from baseline			9
		Abnormal, not clinically significant	37
		Normal	672

Abnormal, clinically significant

Within the Midazolam Injection AI treatment dataset there were four "CLINSIG" entries of "Abnormal, CS", see Figure 2, Figure 3 and Table 5. The event of GGT elevation is associated with an elevated baseline with a small post baseline increase that is not clinically meaningful. There are two events of a decline in hemoglobin value. Subject (b) (6) had a 19% decline in hemoglobin from pre-treatment to 7 hours post treatment. This subject was then found to have a value of 15.8 g/dL at 30 hours post treatment. This represents an increase over baseline. The rapid decline and return to greater than baseline may represent a laboratory error. The clinical significance of this rapid change is uncertain. The next instance of hemoglobin decline was 8.7%

below baseline. This small change may be due to hydration state or background variation. The final "Abnormal, CS" entry for hemoglobin has a post-treatment improvement over the baseline value and is not considered further.

Table 5 Instances of "Abnormal, Clinically Significant in the Midazolam AI Laboratory Dataset of Chemistry and Hematology Studies

SUBJID	Baseline	Sample value	Change	% CHG from Baseline	RR low	RR High	Sample time
(b) (6)	107	115	8	7.5	0	73	30 hr post-dose
	15.3	12.4	-2.9	-19	13.5	17.5	7 hr post-dose
	12.7	11.6	-1.1	-8.7	13.5	17.5	1-2 hr pre-dose
	11.6	11.9	0.3	2.6	13.5	17.5	7 hr post-dose

Reviewer Comment: the frequency of post baseline laboratory values with an entry of "Abnormal, clinically significant" was low with only 4 entries captured in the autoinjector treatment period. None of these events represents a laboratory safety signal causally linked to the autoinjector product.

Abnormal (*value*), not clinically significant

Section 1: Laboratory Values Greater than 25% Decline from Baseline

Clinical Chemistry

The Applicant's laboratory dataset (ADSL) includes a variable CLINSIG with categorical entries of "Abnormal, clinically significant", "Abnormal, not clinically significant", and "normal". The subset of all ADLB entries from the study period of midazolam AI and EOS entries where period 2 was the assigned AI treatment was examined for values of the CLINSIG variable. In this analysis, there were 427 entries with the categorical entry "Abnormal, not clinically significant". From among these 427 entries, there were 58 entries where any post treatment Clinical Chemistry laboratory value had greater than a 25% decline from baseline.

From among those Clinical Chemistry values where decline from baseline was greater than 25%, the laboratory tests for Alanine Aminotransferase, Albumin, Alkaline Phosphatase, Blood Urea Nitrogen, Creatinine, Gamma Glutamyl Transferase, Protein, and Total Bilirubin were excluded from analysis of low value due to the clinical uncertainty of interpretation of low values for these metrics or the low likelihood that a meaningful transition would occur in the 30 hour study period sampling interval. Serum calcium, glucose, bicarbonate and potassium were retained for analysis due to the potential for a clinically meaningful decline to occur in the 30-hour sampling period, see Table 6.

Table 6 Deleted from analysis Chemistry Values, decline from baseline >25% (from AI-ABN, NCS).

Deleted			Retained	
Laboratory Parameter	# Entries	Reason	Laboratory Parameter	# Entries
ALP	4	Low value of uncertain / uncommon clinical significance	CALC	5

Deleted			Retained	
ALT	3	Low value of uncertain / uncommon clinical significance	GLUC	4
BILI	3	Low value of uncertain / uncommon clinical significance	HCO3	4
BUN	3	Low value of uncertain / uncommon clinical significance	K	6
CREAT	2	Low value of uncertain / uncommon clinical significance		
ALB	5	Low value of uncertain / uncommon clinical significance		
TP	5	Low value of uncertain / uncommon clinical significance		

There were 7 subjects identified with 21 entries where a clinical chemistry result during the Midazolam Injection AI period that had a >25% decline from a normal baseline was observed in the results of serum calcium, glucose, bicarbonate or potassium measures. Analysis of the laboratory values reveals that the low values were seen after a sharp decline from pre-treatment to the 7-hour post treatment interval with an increase in value at 30 hours post Midazolam Injection AI treatment. These rapid changes do not have a plausible causal relationship to the midazolam AI, see Table 7. Overall, analysis of the clinical chemistry parameters, with a low shift from baseline of > 25%, that are likely to inform the safety assessment over a 30-hour post treatment interval do not reveal a clinically meaningful safety signal while the two events of hypoglycemia at the EOS measurement do not have a plausible causal relationship to the Midazolam Injection AI treatment because of the prolonged latency to the hypoglycemic events (13 days or more).

Table 7 Assessment of Abnormal, not clinically significant entries with decline from baseline >25%.

SUBJID	Ca++	GLUC			HCO^3	K+
(b) (6)	nadir of 5.8mg/dl @ 7 hrs, increase to 9.6mg/dl @ 30 hours	66mg/dl @ 7 hrs, 113@ 30 hrs			nadir of 18mmol/L @ 7 hrs, return to 23mmol/L at 30 hours	nadir of 2.4meq/L @ 7 hrs post dose, 3.2meq/L at 30 hours
	Nadir of 6.2mmol/L @ 7hrs, 9mmol/L at 30 hours, greater 7hr decline with needle-vial	no value with >25% decline			no value with >25% decline	Nadir of 2.4meq/L @ 7hrs, 4.4meq/L at 30hr, greater 7hr decline (2.0meq/L) with needle-vial
	Nadir of 4.9mg/dl @ 7hrs, 8.3mg/dl @ 30 hours. Low pre-dose of 6.4mg/dl noted in needle-vial treatment period	no value with >25% decline			Nadir of 18mmol/L @ 7 hrs, return to 25mmol/L at 30 hours	no value with >25% decline
	no value with >25% decline	Nadir of 53 mg/dl @ 30 hours with 106mg/dl @ 7 hours, no AE reported			no value with >25% decline	no value with >25% decline
	no value with >25% decline	Nadir of 62 mg/dl @ 72mg/dl@ 7 hours, almost linear decline from 74mg/dl to 66mg/dl			no value with >25% decline	Low baseline of 4.8mmol/L, 4.0@ 7 hrs and 3.4 @ 30 hours (no clear mechanism to explain) reduction seen to 4.2mmol/l with needle vial
	no value with >25% decline	no value with >25% decline			nadir of 12mmol/L @ 7hrs, return to WNL, 22mmol 30hrs	nadir of 1.7 mmol @ 7hrs, 3.5mmol/L @ 30 hrs. non plausible decline, lab error?
		Date	Time	Mmol/L		
		(b) (6)	30hr post Rx	83		

(b) (6)		(b) (6)	EOS	17		
	Nadir of 6.6 mg/dl @ 7 hrs, WNL 9.8mg/dl @ 30 hrs	Date	Time	Mmol/L	nadir of 19mmol/L @ 7hrs, return to WNL, 28mmol 30hrs. non plausible decline, lab error?	nadir of 2.7 mmol @ 7hrs, 3.7mmol/L @ 30 hrs. non plausible decline, lab error?
		(b) (6)	1-2hr pre-dose	93		
			7hr post Rx	71		
			30hr post Rx	62		
			EOS	33		

Hematology

There were 3 subjects with 3 results identified during the Midazolam Injection AI period or at the end of study laboratory sampling where the autoinjector assignment was period 2 (second treatment sequence), with a laboratory result for measurement of Neutrophils, Hematocrit, Hemoglobin, Neutrophils, Platelets, Red Blood Cells, White Blood Cells, lymphocytes, or White Blood Cells that had a greater than 25% decrease from the baseline value. These laboratory tests identified with a greater than 25% decrease were identified in the neutrophils, lymphocytes, or WBC measurements, each in one subject. Two of these values were less than 6% below the lower reference range limit for the laboratory parameter. The remaining value was a measure of lymphocytes at 7 hours post treatment with a value of 0.6 x10^3/uL where the value returns to WNL of 0.8 x10^3/uL at 30 hours post treatment. An almost identical decline from baseline value is observed in the needle from vial administration study period of the same subject. This rapid decline and recovery seen in both treatment periods is not a clinically meaningful safety signal.

Section 2: Laboratory Values Greater than 25% over Baseline

Clinical Chemistry

There were 7 subjects with 9 results identified during the Midazolam Injection AI period or at end of study where the autoinjector assignment was period 2, where the laboratory result for measurement of Alkaline Phosphatase, Total Bilirubin, Aspartate Aminotransferase, Total Bilirubin, Creatinine, was >25% over baseline value and assigned by the Applicant as “Abnormal, NCS”. All of these results were also OORR high.

Subject (b) (6) had an Aspartate Aminotransferase elevated greater than 25% over baseline, however the maximum elevation was 1.2 X ULN and is not evaluated further. Likewise subject (b) (6) had an Aspartate Aminotransferase elevated greater than 25% over baseline, however the maximum elevation was 1.4 X ULN and is not evaluated further. Subject (b) (6) had an Alkaline Phosphatase elevated greater than 25% over baseline, however the maximum elevation was 1.4 X ULN and is not evaluated further. Subject (b) (6) had elevations of total bilirubin of 25% or more over baseline. The baseline, 7-hour, 30-hour post treatment and end of study values for total bilirubin were 0.9mg/dl, 0.8mg/dl, 1.7mg/dl and 1.2mg/dl respectively. These results show a smooth elevation and decline of total bilirubin in a temporal profile associated with the Midazolam Injection AI treatment; the clinical significance is uncertain. There was a 54% increase in AST over baseline at 30 hours post treatment, but this did not

result in an elevation over the reference range high value. There was no elevation of ALT above the ULN, and the maximum elevation of total bilirubin occurred at 30 hours post treatment. A graphic profile of the ALT, AST, ALP and bilirubin values at pre-treatment, 7 hours post treatment, 30 hours post treatment and end of study is seen in Figure 4.

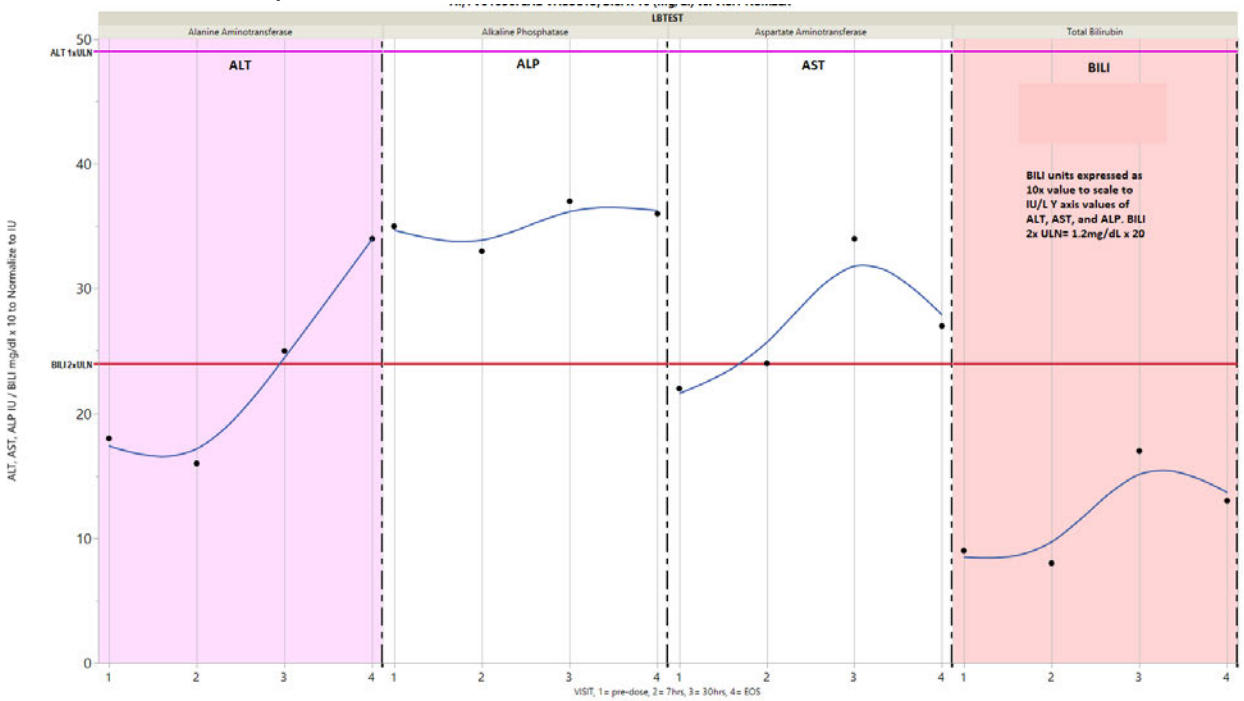
Subject (b) (6) had an elevation of creatinine > 25% over baseline at 7 hours post treatment with Midazolam Injection AI. This value is .05mg/dL greater than the ULN or 4.5% over the upper reference range limit. The values at 30 hours and end of study are within normal limits.

Subject (b) (6) had an elevation of Aspartate Aminotransferase. 25% over baseline at 30 hours post treatment with midazolam delivered by autoinjector. This value was 1 IU over the reference range ULN and was not examined further.

Subject (b) (6) had an elevation of Aspartate Aminotransferase > 25% over baseline at 7 hours post treatment with Midazolam Injection AI. This value was 1.35 x ULN while the 30-hour post treatment and EOS values were 36 IU/L and 27 IU/L respectively. The upper limit of normal is 34 IU/L.

APPEARS THIS WAY ON ORIGINAL

Figure 4 Subject (b) (6), Profile of ALT, ALP, AST and BILI Values from Pre-Treatment to End of Study (EOS), BILI Values X 10 to Scale to IU/L Y Axis Values



Hematology

There were 2 subjects that received Midazolam Injection AI who had 6 entries in the laboratory category "Hematology" where the result was greater than 25% greater than the baseline value. In both of these subjects the greater than 25% over baseline results all occurred at the end of study value. These 2 subjects were assigned to autoinjector treatment in period 2 of the study therefore the EOS value follows Midazolam Injection AI treatment.

Subject (b) (6) had elevations greater than 25% over baseline results for lymphocytes, monocytes, neutrophils, and WBC at the EOS measurement. All of these values were OORR high. All prior results at pre-treatment, 7 hours post treatment, and 30 hours post treatment were within the reference range. The EOS sample was obtained 11 days after the final period 2 measurement. A causal relation between autoinjector treatment and these hematology abnormalities is not supported due to the notable delay of temporal relationship.

Subject (b) (6) had elevations greater than 25% over baseline results neutrophils and WBC at the EOS measurement. Both of these values were OORR high while prior results at pre-treatment, 7 hours post treatment, and 30 hours post treatment were within the reference range. The EOS sample was obtained 13 days after the final period 2 measurement. A causal relation between Midazolam Injection AI treatment and these hematology abnormalities is not supported due to the notable delay of temporal relationship.

Reviewer Comment: Analysis of the clinical chemistry and hematology values are in alignment with the applicant's reports of clinically significant and non-clinically significant results of the Midazolam Injection AI post treatment period. The methodology where values that were greater or less than 25% from baseline were captured for examination proved to be an enhancement of the applicant's summary results from Table 12-7 of the CSR. This was demonstrated by the identification from within the applicant's assignment of NCS (not clinically significant) of the more notable divergences from low or high reference range limits for further analysis. There was no evidence of a new or worsening safety signal associated with midazolam treatment with the Midazolam Injection AI product.

4. Summary

The OCP review team concluded that the PK study conducted by the applicant provided an adequate scientific bridge for this application to rely on the relevant labeling information of LD Seizalam. There was an instance of no quantifiable concentrations of Midazolam or 1'-hydroxymidazolam following treatment Period 1 in a single subject. A study site investigation was unable to identify the underlying basis as an operator error or device malfunction. The safety review did not identify evidence of a new or worsening safety signal associated with midazolam treatment with the autoinjector product.

5. Recommendation

The clinical review, in conjunction with the conclusions of the OCP review team that an adequate PK bridging study was performed supports a recommendation for approval of Midazolam autoinjector for the treatment of status epilepticus in adults.

Appendix: RLM-559-01 Subject (b) (6) Period 1 Dosing Review

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEVEN T DINSMORE
08/05/2022 10:57:49 AM

PHILIP H SHERIDAN
08/05/2022 11:27:47 AM