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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Dantrolene Sodium
(Proposed) Trade Name	Ryanodex Suspension for Injection
Therapeutic Class	Skeletal muscle relaxant
Applicant	Eagle Pharmaceuticals, Inc.
Formulation(s)	Lyophilized powder
Dosing Regimen	Intravenous push beginning at a dose of 1 mg/kg and continuing until resolution or the maximum cumulative dose of 10 mg/kg
Indication(s)	Prevention and treatment of malignant hyperthermia
Intended Population(s)	Adult and pediatric surgical patients who experience malignant hyperthermia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A recommendation of Approval is made for this new drug application. The Applicant has provided adequate evidence that the product will be efficacious and the benefits will outweigh the risks for both of the indications sought, i.e., the prevention and treatment of malignant hyperthermia, when used as proposed in the label.

1.2 Benefit Risk Assessment

The Applicant has relied upon the Agency's previous findings of safety and efficacy for dantrolene sodium by referencing the new drug application for Dantrium (NDA 018264), which was approved for the same indications sought for Ryanodex, i.e., the prevention and treatment of malignant hyperthermia. To this end, the Applicant has conducted a safety, tolerability, and pharmacokinetic (PK) trial in healthy volunteers that compared Ryanodex to the approved Dantrium injection formulation. The PK findings from this trial indicated that, when dosed by weight, the exposure to dantrolene was equivalent for the two products based on the calculations of areas-under-the-curves (AUCs) for plasma levels over time. The PK findings also indicated that C_{max} for Ryanodex was approximately 40% greater than that of Dantrium and that T_{max} for Ryanodex occurred approximately 14 minutes sooner than that of Dantrium. Based on the equivalent dantrolene exposures for the two products, the Agency's previous finding of efficacy for Dantrium can be extrapolated to Ryanodex. The trial is described in detail in Section 9.4.2, and the PK findings are summarized in more detail in Section 4.4.3.

The Applicant also conducted an animal efficacy study, described in Section 4.3, in which Ryanodex, Dantrium and a normal saline placebo were used to treat anesthesia-induced malignant hyperthermia episodes in susceptible swine. The study demonstrated greater survival with Ryanodex and Dantrium treatments than with placebo; indeed, all placebo-treated animals died, and with the exception of a single Ryanodex-treated animal, all of the Ryanodex and Dantrium animals survived. The study also showed that the time to resolution of an episode of malignant hyperthermia were similar for Ryanodex and Dantrium on a dose-by-weight basis, and that both the 2.5 and 10 mg/kg doses were effective for resolving the malignant hyperthermia episode with a 6 minute increase in the median time to resolution for the 10 mg/kg dose of Dantrium versus the 2.5 mg/kg dose, and no difference in the median time to resolution for the two Ryanodex dose groups. In summary, the study showed Ryanodex to be efficacious compared to placebo, and to be similar to Dantrium in its pharmacodynamics.

The substantially greater C_{max} for dantrolene that was measured following Ryanodex treatment, compared to Dantrium treatment, in combination with the equivalent AUCs for the two products, raised the potential for a difference in the safety profiles for the two products. This possibility was addressed by the Applicant by characterizing the safety profile of Ryanodex in several animal models and in healthy volunteers.

The nonclinical safety program included an evaluation of cardiovascular safety of Ryanodex in anesthetized non-MH susceptible swine, 14-day repeat-dose general toxicology studies in dogs and minipigs, a safety evaluation in MHS-swine that received Ryanodex during an MH crises, local tolerance evaluations in rabbits, and an in vitro evaluation of hemolytic potential of Ryanodex due to its 150-fold increased concentration of dantrolene sodium relative to Dantrium. Based on these studies, the Pharmacology-Toxicology review team concluded that there were no safety signals unique to Ryanodex that needed to be evaluated in humans and that the animal data supported the safety of clinical dosing up to the maximum labeled dose of 10 mg/kg based on adequate safety margins from the minipig toxicity study. They also noted that the dog toxicity study and the efficacy study in MHS swine showed that the toxicity profiles for Ryanodex and Dantrium appeared to be comparable. These data are discussed in more detail in Section 7.2.3 below.

The human safety and tolerability trial characterized the risk profiles for Ryanodex and Dantrium at doses up to 2.5 mg/kg, which was the maximum tolerated dose in conscious volunteers. As described in Section 7, there were no safety concerns raised by any of the clinical laboratory assessments made during the trial for either Dantrium or Ryanodex. These assessments included blood chemistries, renal and hepatic function, complete blood counts and differentials, coagulation profiles, arterial blood gas analyses, and electrocardiogram analyses. Similarly, there were no clinically relevant changes in vital sign parameters that occurred with the two treatments. The adverse event profiles for the two products showed that adverse events were mild to moderate for both products, when Ryanodex was infused over the course of a minute or longer, and that they generally resolved within a few hours without intervention. None of the adverse events were considered life-threatening. There was a difference in adverse events that have been reported for Dantrium in its labeling. Specifically, weakness, dizziness and somnolence were observed much more frequently with Ryanodex and were not attributable to hemodynamic changes. The events occurred more frequently and severely when the Ryanodex was infused over 30 seconds, the shortest infusion rate evaluated; they were not dose dependent. These adverse events could be problematic in awake patients being treated prophylactically prior to surgery; however, they will be in a monitored environment and can be easily confined to bed rest, unless assisted, when the drug is used in this fashion. These events would not be problematic for a patient being treated during an MH crisis whether it occurs during an anesthetic or following the anesthetic as the patient will be confined to bed for continuous monitoring for 24 hours to assure the crises has completely resolved. In summary, the human data indicate that Ryanodex and Dantrium are similarly safe in terms of routine clinical

assessments, but some of the dantrolene-associated adverse reactions, none of which are life-threatening, that have been reported for Dantrium may occur more frequently in Ryanodex-treated patients.

A last point that bears some consideration in the benefit-risk analysis relates to the time required to reconstitute and administer the two formulations of dantrolene. As described in the Summary of Safety Section, the differences in time required to reconstitute and administer Dantrium and Ryanodex may be substantial, possibly 10-20 minutes depending on the dose required. The time saved by using Ryanodex is time that can be spent instituting the multiple supportive measures needed to reduce morbidity and mortality and making the clinical evaluations necessary to guide therapy. In this regard, Ryanodex offers a benefit over Dantrium; the extent of which is not known.

In summary, the Applicant has provided sufficient evidence that the efficacy of Ryanodex is equivalent to that of Dantrium when the two products are dosed by weight. They have also shown that the differences in the safety profiles of the two products lie in the frequency of dantrolene-associated reactions, which pose no substantial risk for morbidity or mortality provided patients are appropriately monitored and permitted to ambulate only with assistance for an appropriate period, following administration of the drug product. Overall, the benefits of Ryanodex clearly outweigh the risks when the product is used for prophylaxis or treatment of malignant hyperthermia.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At this time, there are no recommendations for postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

At this time, there are no recommendations for postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Malignant hyperthermia (MH) is a genetically transmitted, autosomal dominant, potentially fatal, hypermetabolic condition. An MH episode can be triggered by exposure to the volatile, halogenated, anesthetic agents and the depolarizing muscle relaxant succinylcholine. Common signs of an episode include muscle rigidity, hyperthermia, tachycardia, increased oxygen consumption and carbon dioxide production, acidosis, and rhabdomyolysis. It is estimated that approximately 1 in 3000 individuals carries a defective ryanodine receptor gene, which renders them susceptible to the condition. The incidence of MH episodes following a general anesthetic that included a triggering agent has been estimated to be from 1 in 5,000 to 1 in 100,000 anesthetics.

Treatment of an MH episode includes:

1. Discontinuation of the triggering agent.
2. Rapid administration of dantrolene sodium.
3. Initiation of aggressive supportive care that includes hyperventilate with 100% oxygen, treatment of metabolic acidosis, cooling of the patient, treatment of dysrhythmias and hyperkalemia, and maintenance of urine output with diuretics to reduce the risk of kidney injury secondary to myoglobinuria.

Prior to the introduction of the intravenous dantrolene in 1979, mortality from malignant hyperthermia was over 60%; following the introduction of dantrolene, mortality has been estimated to be less 5%. Most of the reduction in mortality is considered to be due to the availability of dantrolene; however, better recognition of the signs of an MH episode in its early stages and more aggressive intervention with supportive care may have also contributed to the improved outcomes. There are no uniformly accepted criteria for defining the onset of an MH episode, and increases in core body temperature is often a later sign. Thus, making the diagnosis of an MH episode and the decision to intervene are clinical judgments whose timing may have a significant impact on the morbidity and possible mortality for the patient.

The currently available formulation of dantrolene sodium is a vial that contains dantrolene sodium 20 mg and mannitol 3000 mg as a diuretic. When reconstituted, the total volume of the product is 60 ml, and the concentration of the dantrolene sodium is 0.33 mg/mL. The dose of dantrolene sodium required to treat the MH episode varies depending, in part, on the severity and persistence of MH symptoms. Doses of dantrolene sodium are started at a minimum of 1 mg/kg; although 2.5 mg/kg starting doses are not uncommon in clinical practice. The highest recommended dose is 10 mg/kg. Given the low concentration of dantrolene sodium in each vial of the currently available products and the need to reconstitute each vial with 60 mL of sterile water for

injection, a considerable amount of time is required to administer the treatment to a patient during a life-threatening situation that requires numerous other interventions to minimize the risks of morbidity and mortality. In this regard, the development of Ryanodex may offer a benefit. Ryanodex is a novel, lyophilized formulation of dantrolene sodium that forms a microcrystalline dispersion when it is reconstituted, at which time, each vial contains 250 mg of dantrolene sodium in 5 mL of sterile water, a 50 mg/mL suspension that substantially expedites the administration of each dose of the treatment compared to the currently available formulation.

The excipients contained in Ryanodex include mannitol (25 mg/mL), Polysorbate 80 (5 mg/mL) and Povidone (0.8 mg/mL). It is important to note that the amount of mannitol in Ryanodex is substantially less than that contained in Dantrium. With Dantrium, the mannitol serves as a diuretic, which is needed to reduce the risk of renal injury following an episode of malignant hyperthermia and the myoglobinuria that ensues. Therefore, it is recommended that the Ryanodex label clearly indicates that the amount of mannitol is insufficient to produce the level of diuresis needed to ensure renal protection and that clinicians should select a diuretic, based on the patient's clinical status and underlying medical conditions, for use with Ryanodex.

2.2 Tables of Currently Available Treatments for Proposed Indications

The only available treatment for either the treatment of or prophylaxis for malignant hyperthermia is dantrolene sodium, which is currently marketed in the United States under the name Dantrium, which has been approved in both injectable (NDA018264) and capsule (NDA017443) forms. There are generic products available for both formulations as well.

2.3 Availability of Proposed Active Ingredient in the United States

The drug substance, dantrolene sodium, (b)(4), USP is manufactured by (b)(4). There is no known limitation to the supply of dantrolene sodium to either this manufacturer or the manufacturers of the currently marketed products.

2.4 Important Safety Issues with Consideration to Related Drugs

Most of the known safety issues related to dantrolene appear to be related to its mechanism of action as a muscle relaxant agent. The Dantrium label states the following regarding muscle weakness occurring with the use of the product:

Based upon data in human volunteers, it will sometimes be appropriate to tell patients who receive Dantrium Intravenous that decrease in grip strength and weakness of leg muscles, especially walking down stairs, can be expected postoperatively. In addition, symptoms such as "lightheadedness" may be noted. Since some of these symptoms may persist for up to 48 hours, patients must not operate an automobile or engage in other hazardous activity during this time. Caution is also indicated at meals on the day of administration because difficulty swallowing and choking has been reported.

Additional safety concerns that are described in the Dantrium IV label include:

1. Injection site injury following extravasation of the product into the surrounding tissues due to the high pH of the intravenous formulation.
2. Hepatotoxicity has occurred with use of the capsules when administered for prolonged periods of time, i.e., several months.
3. Drowsiness and dizziness
4. Pulmonary edema developing during the treatment of malignant hyperthermia crisis in which the diluent volume needed to deliver dantrolene possibly contributed.
5. Thrombophlebitis
6. Urticaria and erythema
7. Anaphylaxis.
8. In addition, there are serious reactions that have been reported with long-term oral Dantrium use including hepatitis, aplastic anemia, seizures, and pleural effusion with pericarditis, leukopenia, lymphocytic lymphoma, and heart failure.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Division and the Applicant had three meetings during the clinical development program, which was conducted under PIND/IND 105411. The key points from each of the meetings are summarized below.

On July 23, 2009, a Pre-IND Meeting was held. The following issues were discussed at that time:

1. The application of the Animal Rule for Ryanodex as a treatment for malignant hyperthermia was appropriate, and it was acceptable to seek approval of Ryanodex by submission of a 505(b)(2) NDA.
2. A Ryanodex formulation with a level of Povidone K12 that exceeds the total daily intake of an approved product would require nonclinical toxicity studies to assess the risks; however, such studies may not be required if the supplier of Povidone K12 has included toxicology information in their DMF that are supportive of the levels in the Ryanodex formulation.
3. The particle size distribution (PSD) of povidone must be shown not have an impact on the manufacture of the final product.

4. Although (b) (4) particles are less than (b) (4) in diameter, and the dissolution time is about (b) (4), either a limit test needs to be conducted or the time to reconstitution to a solution needs to be provided.
5. The Division provided the following information to guide the design of animal studies:
 - a. The Agency's standards for assessing safety and efficacy cannot be lowered based on the number of animals available to study.
 - b. Dantrolene has already been determined to be an effective antidote thereby reducing the evidence required to demonstrate the efficacy.
 - c. The pig study x requires a comparator arm to confirm efficacy of the formulation, establish a minimally effective dose, and characterize the safety profile.
 - d. Understanding the differences between Dantrium and Ryanodex will be important.
 - e. For a study utilizing 20 pigs, there should be a placebo arm and a low-dose (1 mg/kg) and high-dose (10 mg/kg) treatment arm for both Ryanodex and Dantrium.
 - f. This allotment of animals would likely provide the data need to support an NDA approval for Ryanodex, i.e., the demonstration of efficacy compared to placebo, establishment of a minimally effective dose, and characterization of the safety profile over a range of doses. In addition, this paradigm would provide the information that would allow the label for Ryanodex to be appropriately modified from that of Dantrium in terms of identifying substantial differences in dosing, in use of supportive measures taken to treat an MH crisis and its sequelae, and in the safety profile.

On January 26, 2011, an End-of-Phase 2 Meeting was held. The following are the key points discussed at that meeting:

1. The level of Povidone K12 had been adequately qualified for Ryanodex.
2. The Sponsor was to provide a separate characterization test for the time that the product dissolves in medium at a certain pH in addition to quality control dissolution test.
3. A validated method with a proper reference was needed for monitoring particle size distribution. The particle size specification for the drug product was not acceptable due to clinical safety concerns. It was necessary to determine the fate of the particles following administration. It was necessary to know how many particles are greater than (b) (4).
4. There was agreement that the calculation of the weight of the API may be based on the (b) (4) formulation as it is with Dantrium and in the USP monograph.
5. The Sponsor was to examine ways to increase the dose in animal models to achieve toxic levels and to provide an assessment of the margin of safety that exists, if any, for the proposed human doses.

6. There did not appear to be any evidence that a 1 mg/kg dose of Ryanodex would be less efficacious than the 1 mg/kg dose of Dantrium. Therefore, without a justification for doing otherwise, the label for Ryanodex, if it is approved, would include the 1 mg/kg initial dose.
7. The overall design of the pivotal trial, i.e., blinded, placebo- and active-controlled, was appropriate for the evaluation of efficacy and would be suitable for filing purposes.
8. After a preliminary review of the data in the pivotal efficacy study in the MH susceptible swine, it appeared that there may be differences in the PK characteristics of dantrolene related to the formulation, i.e., Ryanodex or Dantrium. Since the two formulations differed significantly in terms of drug concentration and, therefore, total infusion times and total volumes of infusion, it was important to characterize a safe dosing regimen in humans. Therefore, a single-dose study in humans needed to be conducted to compare the PK and safety of Ryanodex (and its major metabolite, 5-hydroxydantrolene) to that of Dantrium. The PK findings will be used to verify whether the toxicology studies and animal efficacy study support the proposed upper limit of dosing in humans. The safety data will provide important information on whether Ryanodex has safety profile characteristics that need to be considered by clinicians when selecting an antidote for a given patient, both in the setting of prophylaxis and of treating MH episodes.
9. As there have been side effects reported in the administration of Dantrium to healthy volunteers (e.g., decrease in grip strength, weakness of leg muscles, especially walking down stairs, lightheadedness and difficulty swallowing and choking), one of two approaches should be taken for the clinical study.
 - a. Ideally, subjects could be drawn from the population of patients presenting for surgery who will need MH prophylaxis at the time of their operation. The PK and safety data from this population would reflect that of clinically relevant dosing. The benefits these subjects will gain from the dantrolene therapy would outweigh the risks for both treatments, assuming the animal studies for Ryanodex support the dose to be used.
 - b. Alternatively, healthy volunteers could be evaluated; however, doses less than those to be used in the clinical setting would likely be required to minimize the risk to the subjects for whom there will be no benefit from exposure to the drug products. The PK data from this population will resolve the issues described above, but the safety data may be less meaningful due to the reduction in dose. The alternative approach should be used if the time to recruit patients requiring prophylaxis would be prohibitively long.
10. It was possible that this application may require the input of an Advisory Committee to obtain expert feedback regarding the adequacy of the animal and human data for supporting findings of safety and efficacy.

The IND was opened on June 29, 2012, with submission of the protocol for the safety, tolerability, and pharmacokinetics trial to be conducted in healthy volunteers. The trial was allowed to proceed after some minor modifications were made to the protocol.

The last meeting with the Sponsor was the Pre-NDA Meeting that occurred on August 7, 2013. At that time, the following issues were discussed:

1. The proposed control strategy for particle size distribution appeared reasonable.
2. The determination of the saturation solubility of dantrolene sodium in the dissolution medium and characterization of dissolution at earlier time points were acceptable. However, the proposed dissolution acceptance criterion but had to be evaluated in the context of the totality of the in-vitro dantrolene dissolution data.
3. Given the high pH of the solutions during filling and after reconstitution, and that (b) (4) can also be leached out from the glass vials, it was recommended that the Sponsor conduct a one-time study in which the (b) (4) content of the suspension was measured 6 hours after reconstitution. If the content of (b) (4) was well below the safety threshold, it would be acceptable not to monitor it in commercial batches of the product.
4. Regarding the proposal to include data related to (b) (4) in the NDA, the Division stated that, in the absence of a sufficient justification, these data should be omitted from the NDA, unless a safety signal is detected that might have implications for the use of Ryanodex to treat malignant hyperthermia.
5. Based on the studies that had been conducted to generate evidence of the product's safety and efficacy as compared to Dantrium, it was believed that a 505(b)(2) submission would be feasible.
6. Providing information on linearity of PK parameters and safety observations associated with the anticipated higher C_{max} with Ryanodex were needed to help understand its safety profile.
7. The following were to be included in the NDA submission:
 - a. Bioanalytical method validation information for analytical methods used to analyze dantrolene in systemic circulation.
 - b. Descriptive statistics of dantrolene PK parameters. Although bioequivalence cannot be achieved, a bioequivalence analysis for C_{max} and the AUC of dantrolene following Ryanodex administration compared to Dantrium should be presented.
 - c. Electronic datasets.
8. For a 505(b)(2) application not submitted under Subpart H or I, if the PK parameters of the new product are nearly identical to those of the referenced product, it can be inferred that the efficacy and safety of the two products should also be identical. Without the actual data, it is not possible to determine how well the PK characteristics of Ryanodex match those of Dantrium. If the PK profiles for the two products are not identical, or nearly so, additional information may be required. In this situation, one of the following two alternatives would apply:

- a. If dantrolene exposure with Ryanodex is less than with Dantrium, it raises the question as to whether Ryanodex is as effective as Dantrium, and evidence of efficacy would be required. With less exposure, it would be expected that Ryanodex poses less risk and, therefore, the amount of safety data required for the benefit-risk analysis would be similarly reduced.
 - b. If dantrolene exposure with Ryanodex is more than with Dantrium, this would raise the question as to whether Ryanodex poses additional risk compared to Dantrium. The extent to which the C_{max} differed would determine the amount of safety data needed to adequately characterize the risk profile. Therefore, it will be important to justify the size of your safety database in terms of it being adequate to characterize the risk profile of Ryanodex. In this regard, drawing on the safety findings for the two products in your nonclinical studies, the known risks identified by the long history of Dantrium use, the extent to which the two products were similar in your safety assessments, and the extent to which safety was evaluated at the highest tolerated doses will be important components of your rationale for the size of the safety database. This rationale should be incorporated into the ISS.
9. The Division informed the Sponsor that they will likely need additional human safety data as the number of subjects in the PK study is not adequate to characterize the risks associated with Ryanodex. The extent to which the PK profile of Ryanodex differs from that of Dantrolene will determine, in part, the size of the safety database. While knowing the AUCs for the two products is helpful, the higher C_{max} for Ryanodex might pose an additional risk, depending on the magnitude of the difference, and that would need to be determined prior to the NDA submission. Therefore, the Division suggested that, along with the detailed clinical pharmacology summary statistics and accompanying human subject safety data, submission of a summary of the animal histopathology data including a comparison to Dantrium would be helpful in making a safety database size determination.

2.6 Other Relevant Background Information

There is no other relevant background information for this application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality and well enough organized with complete datasets to allow meaningful review. The various sections of the NDA and supporting documents were consistently arranged according to eCTD standards with functional links to appropriate references.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in compliance with Good Clinical Practices. For each of the pivotal studies, the Applicant included the statements:

This study was performed in accordance with Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) final guideline (May 1996) including the archiving of essential documents.

3.3 Financial Disclosures

The Applicant certified the following for each of the Investigators involved with the pivotal studies:

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). 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. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(1).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls (CMC) review team included Drs. Yong Hu and Julia Pinto. They concluded that the information provided in the application was adequate to assess the identity, strength, purity, and quality of the proposed commercial product. They found no issues that could preclude an approval of the application provided the Applicant addresses three outstanding issues:

1. Data to support the product administration information in the labeling, i.e., the compatibility with [REDACTED] (b) (4) solutions
2. Stability information for the reconstituted suspension under room light
3. Resolution of carton and container label deficiencies

The Biopharmaceutics review team included Drs. John Duan and Tapash Ghosh. Their concerns regarding dissolution of the product and the potential for its precipitation have been adequately addressed by the Applicant. They note that the dissolution study conducted in human plasma provides evidence, from an in vitro perspective, to support a rapid dissolution of Ryanodex upon exposure to human plasma at a dose of 175 mg. Based on the information available, they recommend approval of the application and have no recommendations for postmarketing commitments or agreements.

From a clinical perspective, it is important that the outstanding compatibility issues be resolved prior to approval of the product as they potentially affect the safety and efficacy of the product should Ryanodex be incompatible with either solution. The other two issues should also be resolved but do not pose as high a level of risk as infusing the product with an incompatible solution.

4.2 Clinical Microbiology

The Clinical Microbiology review was conducted by Denise Miller and Dr. Neal Sweeney. They did not identify any issues that would preclude an approval action. They did include the following post-approval stability protocol and stability commitment in their review:

The first three commercial lots will be placed on stability under the long term storage conditions. Thereafter, one lot annually will be placed in the stability program. Specifications and testing schedule for post-approval stability program is under long term conditions.

- Container Closure Integrity – tested by sterility at 12, 24, 30, and 36 months.
- Endotoxin – tested at 12, 24, 30, and 36 months.
- Microbial Limits - NA

They noted that proposed shelf life is at least 24 months at 25°C and that the post-reconstitution shelf life is not more than 6 hours at 25°C. They indicated that these are acceptable parameters given the data available and that Ryanodex is an emergency use product so there is likely to be minimal storage of the product following reconstitution.

From a clinical perspective, the rationale used by the Clinical Microbiology review team is reasonable. Additionally, the proposed product labeling indicates that the product must be used within 6 hours when stored at controlled room temperature (68°F to 77°F), which will likely minimize the risk of residual product being retained for use in the event of recrudescence of malignant hyperthermia more than 6 hours after the initial episode.

4.3 Preclinical Pharmacology/Toxicology

Drs. Jay Chang and Adam Wasserman conducted the Pharmacology-Toxicology review of Ryanodex. They have not identified any preclinical issues that would preclude an approval action and have no recommendations for additional nonclinical studies following the product's approval. The information that follows comes from Dr. Chang's primary review and provides summary information on the animal efficacy studies conducted in support of this application.

The efficacy and safety of Ryanodex were characterized using malignant hyperthermia susceptible (MHS) swine in four pilot studies and one pivotal study. The pilot studies were designed to optimize instrumentation, blinding, and sample collection procedures as well as gather some efficacy data. The general study design was similar for all five studies and included the following:

1. On Study Day (SD) 1, animals were surgically prepared, MH episodes were induced by exposure to 1-2% halothane or 4% sevoflurane (used in pivotal study), with an additional 1 or 2 mg/kg IV succinylcholine injection if treatment with the inhalational agent alone failed to induce an episode.
2. The onset of the MH episode was defined as the presence of at least two of the following criteria:
 - a. End-tidal carbon dioxide (CO₂) ≥ 70 mmHg
 - b. Arterial pCO₂ ≥ 75 mmHg
 - c. Arterial pH ≤ 7.20
 - d. Tachycardia (≥ 40% increase above baseline heart rate)
 - e. Occurrence of cardiac arrhythmia
 - f. Body temperature increase ≥ 1.5°C

g. Muscle rigidity

Full resolution of the MH episode was based on the clinical judgment of a treatment-blinded staff veterinarian who determined that the animal had no life-threatening conditions and that changes in all MH parameters listed above had reversed.

3. After initiation of an MH episode, animals were treated in randomized fashion with Ryanodex, Dantrium, or saline, with or without supportive care, e.g., injection of sodium bicarbonate to adjust blood pH, administration of lidocaine to treat arrhythmia, application of external cooling devices. They were then monitored until MH resolution, death, or euthanasia in extremis.
4. Animals that survived the MH episode were followed for safety and survival typically until SD 6 when scheduled necropsy occurred.
5. Assessments over the course of the studies included reversal of MH symptoms, PK analysis of dantrolene and 5-hydroxydantrolene, its metabolite, and safety evaluations including signs of adverse reactions to treatment, clinical pathology, gross pathology, and histopathology.

In the pivotal study (Study #1773-004), MHS swine received Ryanodex or Dantrium at one of two doses, 2.5 mg/kg or 10 mg/kg, the latter being administered as 2.5 mg/kg four times at 5 minute intervals, or normal saline as a control. All animals also received supportive care. The efficacy endpoints included:

1. Time to MH Resolution (the primary endpoint)
2. Proportion of Subjects Achieving MH Resolution
3. Time to reversal of the first two parameters (F2P) that defined the onset of the MH episode (see item 2 in the list above)
4. Proportion of Subjects Achieving F2P

In the pivotal efficacy study, where an MH episode was triggered by sevoflurane with or without succinylcholine, none of the animals administered saline achieved MH resolution or F2P and all died; whereas, 15 of the 16 (94%) Ryanodex-treated animals achieved MH resolution and F2P, and 16 of the 16 (100%) Dantrium-treated animals achieved MH resolution and F2P. The difference in the proportions of subjects achieving MH resolution between the Ryanodex-treated group and the saline-treated group was statistically significant in favor of Ryanodex ($p = 0.0003$). It was similarly significant in favor of Ryanodex with respect to the event of F2P ($p < 0.0001$). The study was not adequately powered to determine a statistical difference between the Ryanodex and Dantrium treatment groups.

It was noted that a MH episode was not triggered in one animal from the 10 mg/kg Ryanodex group following sevoflurane exposure; this was the only animal that required succinylcholine for induction of MH. Following Ryanodex treatment with supportive care, the animal subsequently reversed most of the MH-defining parameters but failed to reach MH resolution due to persistent muscle rigidity and elevated potassium. At about 2 hours after Ryanodex treatment, the animal had heart rate fluctuations and,

shortly thereafter, had elevation of end tidal CO₂ and PaCO₂ and lowering of arterial pH, indicative of MH recrudescence. An additional 2.5 mg/kg dose of Ryanodex was administered without improvement, and the animal was euthanized in extremis at ~4 hours after the start of treatment. It was unclear why this animal did not respond to treatment and experienced recrudescence of MH.

The efficacy and pharmacokinetic findings from the pivotal study are summarized in Table 1 below.

Table 1. Summary of pivotal efficacy study results (based on the Table on p. 6 of Jay Chang's review)

Treatment	Saline	Ryanodex		Dantrium	
Dose	N/A	2.5 mg/kg	10 mg/kg	2.5 mg/kg	10 mg/kg
	N=5	N=8	N=8	N=8	N=8
MH Resolution					
Proportion of animals achieving MH reversal	0 (0%)	8 (100%)	7 (88%)	8 (100%)	8 (100%)
Time to MH reversal (min)					
Mean	N/A	36	29	40	33
Median	N/A	28	28	21	27
F2P					
Proportion of animals achieving F2P	0	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Time to F2P (min)					
Mean	N/A	19	19	19	16
Median	N/A	17	16	14	13
Survival to SD 6 (termination)	0	7	7	7	7
Pharmacokinetics					
Dantrolene:					
C _{max} (ng/mL)	N/A	6,860	22,912	18,191*	12,781
AUC ₀₋₂₄ (ng·hr/mL)	N/A	9,077	93,608	10,250	111,496
5-Hydroxydantrolene:					
C _{max} (ng/mL)	N/A	400	1,070	517	1,500
AUC ₀₋₂₄ (ng·hr/mL)	N/A	2,811	12,811	3,988	20,106

*Suspected artifact due to blood sampling during Dantrium administration

Janice Derr, Ph.D., from the Division of Biometrics II, reviewed the pivotal efficacy study and performed a statistical analysis of the data. She provided the following insights:

1. For the comparisons of active versus saline treatments, the study had reasonable statistical power, based on the following assumptions:
 - a. A low (~ 1%) chance of recovering from MH episode in saline group (n=5)
 - b. At least 70% chance or greater of recovering from MH episode in the active treatment arm (n=8)
2. The active treatment arms were both superior to the saline treatment arm for the percentage of cases with resolution of the induced MH episode.
3. For a comparison of the Ryanodex versus Dantrium treatments, the study was too small to make useful conclusions.
4. Approximately 130 animals/treatment group would be needed to detect a difference of 10% or greater (absolute) (e.g., between 95% in Dantrium and 85% or less in the Ryanodex) or a difference in the percentage of animals that recovered from an induced MH episode.
5. Ryanodex and Dantrium treatments were similar in the median time to resolution of the MH episode.

From a clinical perspective, the study clearly demonstrated that:

1. Both Dantrium and Ryanodex increased survival, compared to placebo, following an episode of MH.
2. The survival rates for Ryanodex and Dantrium were similar for the two doses studied: 100% for both treatments with a 2.5 mg/kg, and 100% for Dantrium but 88% for Ryanodex at the 10 mg/kg dose.
3. Using the protocol definitions for onset and resolution of an MH episode, the two active treatments were similar in their median times to resolution of the MH episode, between 21 and 28 minutes. The differences in median times to resolution based on the dose administered, i.e., 2.5 and 10 mg/kg, were 6 minutes for Dantrium and 0 minutes for Ryanodex (discounting the animal that died in the 10 mg/kg group).

The Applicant's methods for defining the onset and resolution of an MH episode were artificial, but provided consistency in timing events in the study. In the clinical setting, there is no standard definition for either of these parameters. The diagnosis is based on clinical impression using some of the criteria the Applicant used. The resolution is also based on clinical impression; however, the Malignant Hyperthermia Association of the United States (MHAUS) recommends that dantrolene treatment be continued for at least 24 hours with treatment titrated to alleviation of hypermetabolism (as indicated by hypercarbia or hyperthermia), muscle rigidity, tachycardia, acidosis, and elevated creatine kinase levels.

Overall, the pivotal animal study provided evidence that Ryanodex and Dantrium are similarly efficacious at terminating an MH episode and at increasing survival rates following an MH crisis. The study also demonstrated the two products produced similar outcomes when dosed by weight in dose ranges that are similar to those proposed for use in the clinical setting.

4.4 Clinical Pharmacology

Drs. Nallani and Xu provided the Clinical Pharmacology review for this application. They did not identify any issues that would preclude an approval action, and they have no recommendations for post-approval commitments or requirements.

4.4.1 Mechanism of Action

Malignant hyperthermia (MH) is an inherited, autosomal dominant disorder of skeletal muscle, which presents clinically as a hypermetabolic response to the volatile anesthetic gases and the depolarizing muscle relaxant succinylcholine. Susceptibility is related to a mutation in the gene that codes for the ryanodine receptor 1 (RyR1), which is found in the sarcoplasmic reticulum of skeletal muscle myocytes. Normally, the RYR1 opens in response to increases in intracellular Ca^{2+} levels following muscle contraction and promotes reuptake of calcium back into the sarcoplasmic reticulum thereby allowing muscle relaxation. In MH susceptible individuals, the defect in RyR1 reduces the reuptake of calcium resulting in sustained muscle contractions and the hypermetabolic state associated with an MH episode.

Dantrolene sodium appears to work by its high-affinity, monophasic-inhibition of the RyR1 Ca^{2+} channel, which permits sequestering of Ca^{2+} in the sarcoplasmic reticulum and, ultimately, skeletal muscle relaxation with subsequent recovery from the hypermetabolic state.

4.4.2 Pharmacodynamics

An episode of malignant hyperthermia is marked by a number of major signs that include:

1. Severe hyperthermia (a late sign)
2. Increased oxygen consumption and carbon dioxide production
3. Metabolic acidosis
4. Muscle rigidity
5. Rhabdomyolysis
6. Ventricular dysrhythmias
7. Hyperkalemia
8. Myoglobinuria

There is no consensus regarding which signs are required and how severe they need to be to make the diagnosis of an MH episode. Rather, the diagnosis and the initiation treatment are based on clinical impression of the patient's status and a high level of suspicion that the etiology may be MH.

The treatment of an MH episode is multifactorial and includes discontinuation of the triggering agent(s), rapid administration of dantrolene sodium, and supportive care directed at correcting metabolic derangements and preventing kidney injury secondary to the release of myoglobin that occurs with the breakdown of the skeletal muscle.

It is as difficult to determine when an MH episode has been terminated as it is to determine its onset. Recrudescence has been reported, which makes the initial resolution of the signs an unreliable indicator. In addition, the multimodal treatment approach and need for continued dantrolene sodium treatment to reduce the risk of recurrence confound any effort to pinpoint the time of resolution.

There were no clinical trials conducted to assess the efficacy of Ryanodex; therefore, there was no need to tie the pharmacodynamics of the product to trial endpoints. For the pivotal animal efficacy study, the Applicant chose to identify the onset of an MH episode by the occurrence of the first two signs from a list developed for the study (see Section 4.3 above). The time to resolution of the two signs and the determination, by a treatment-blinded veterinarian, that the episode had resolved were utilized as the efficacy endpoints. While the use of two signs from a list may not reflect clinical practice, the method provided a non-biased and consistent means of making the determination across treatment groups. The veterinarian's determination is more reflective of clinical practice and also provided a consistent means of comparing treatment efficacy. However, these approaches to assessing efficacy are meaningless if there is a difference in mortality as MH is generally lethal if the only treatments are discontinuation of the triggering agents and supportive care. In this regard, both Ryanodex and Dantrium appeared to be similarly efficacious compared to placebo, which was associated with 100% fatality. The remainder of the efficacy assessments indicated that Ryanodex and Dantrium were similar to each other and superior to placebo.

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) study of Ryanodex and Dantrium was important in two regards. First, it defined the PK characteristics of Ryanodex allowing the product to be bridged to Dantrium and the Applicant to seek approval under §505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Second, it determined whether dantrolene exposures with Ryanodex were greater or lesser than, or equivalent to, Dantrium, which in turn, dictated whether the Applicant needed to provide additional safety information, i.e., if the exposure with Ryanodex exceeded that of Dantrium, or provide additional efficacy information, i.e., if the exposure with Ryanodex was less than that with Dantrium.

The Clinical Pharmacology review team noted that the PK study was appropriately designed and conducted, and based on their own analyses, they concurred with the Applicant's findings. They specifically noted the following:

1. Administration of the two treatments in a crossover fashion made mathematical comparison of bioavailability possible despite the differences in the duration of administration, 1 minute infusions for Ryanodex versus 0.15 min/kg infusions for Dantrium.
2. For dantrolene, the 90% confidence intervals (CI) demonstrated that the two treatments were equivalent for AUC_{0-inf} (using a 90% CI criteria of 80-125%).
3. Significant differences between Ryanodex and Dantrium were evident for C_{max} , for which the 90% CI range was 1.18-1.75. This was likely a direct result of the differences in concentrations of the products and the durations of their infusions.
4. The relative bioavailability results demonstrate that AUC_{0-inf} and C_{max} were 6% and 44% higher for Ryanodex as compared to Dantrium based on the geometric mean ratios.

The higher C_{max} for Ryanodex warranted the trial assessing safety and tolerability in healthy volunteers; the equivalent AUC_{0-inf} allowed the extrapolation of the Agency's previous findings of efficacy for Dantrium to Ryanodex. The key PK findings for Ryanodex and Dantrium at the 2.5 mg/kg dose in humans are summarized in Table 2.

Table 2. PK parameters for Ryanodex and Dantrium (based on the table on p. 6 of Srikanth Nallani's review)

PK Parameter	Dose 2.5 mg/kg	
	Ryanodex (N=15)	Dantrium (N=16)
AUC_{0-inf} obs (hr* μ g/mL)		
n	15	16
Mean	78	72
(SD)	(23)	(19)
AUC_{0-last} (hr* μ g/mL)		
n	15	16
Mean	75	70
(SD)	(22.960)	(18.618)
C_{max} (ng/mL)		
n	15	16
Mean	8978	5716
(SD)	(4636)	(1270)
$T_{1/2}$ (hr)		
n	15	16
Mean	11	10
(SD)	(2.2)	(2.4)
T_{max} (hr)		
n	15	16
Median	0.02	0.25
Min	0.0	0.0
Max	1.0	1.5

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There was only one clinical trial planned for this application; however, during the conduct of the trial, amendments to the protocol required the use of a different clinical research organization, and the Applicant opted to begin the trial over again. Thus, clinical trials 1201A, the partly completed trial, and 1201, the completed trial, constitute the only sources of clinical data for this new drug application.

5.2 Review Strategy

This review takes into consideration both the nonclinical studies involving toxicology assessments and the two clinical trials conducted by the Applicant as well as the 120-Day Safety Update for evaluating the safety of Ryanodex. Also taken into consideration are the human pharmacokinetic data bridging Ryanodex to Dantrium for the extrapolation of the Agency's previous findings of efficacy for Dantrium to Ryanodex for both of the indications sought by the Applicant and the pivotal animal efficacy study conducted by the Applicant that compared Ryanodex, Dantrium, and normal saline placebo treatments. The information from both the nonclinical and clinical studies were utilized for performing the benefit-risk analysis that served as the basis for the recommendation for regulatory action.

Input from members of each of the respective review teams regarding relevant information pertaining to safety from the chemistry, preclinical and clinical pharmacology sections of the NDA submission were taken into consideration along with the expertise of the statistical reviewer for the analysis of the efficacy data in pivotal nonclinical efficacy study.

5.3 Discussion of Individual Studies/Clinical Trials

Details of the two trials that provided all of the human safety, tolerability, and pharmacokinetic data can be found in Section 9.4 below. The two trials were similar in overall design but differed in some of the safety assessments that were made.

6 Review of Efficacy

Efficacy Summary

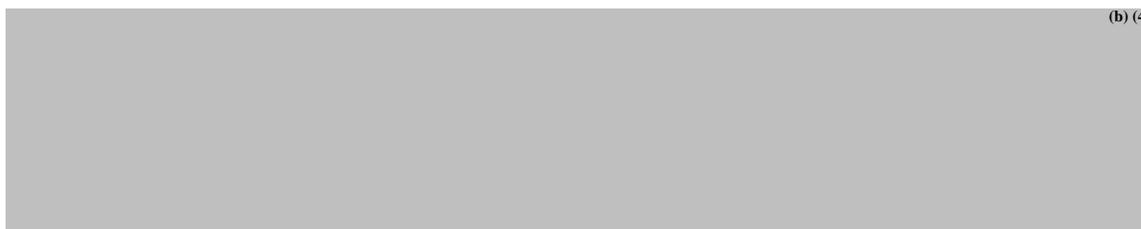
There were no clinical trials conducted that assessed the efficacy of Ryanodex for the proposed indications. Indeed, the only human exposures to Ryanodex occurred in the two trials evaluating the safety, tolerability, and pharmacokinetics of the product. Trial 1201 compared the pharmacokinetics of Ryanodex to those of the approved intravenous formulation of dantrolene, Dantrium IV (Dantrium). The findings from the trial demonstrated that the systemic dantrolene exposures were similar for the two products administered at the same mg/kg dosage, based on area-under-the-curve (AUC) calculations; however, there was a higher C_{max} with Ryanodex than Dantrium. Based on the equivalent exposures at the same doses, the efficacy and dosing of Ryanodex for the prophylaxis and treatment of malignant hyperthermia (MH) can be extrapolated from the Agency's findings of efficacy and dosing recommendations for Dantrium.

The findings for the clinical trial are supported by those of the pivotal animal efficacy study described in Section 4.3 above. The animal study demonstrated that both Ryanodex and Dantrium, administered at the same dose were similarly effective at terminating a malignant hyperthermia crisis and were associated with similar survival rates following an MH crisis. Both treatments were substantially better than treatment with placebo, which failed to terminate the MH crisis and resulted in the demise of all the animals in that treatment group. The other efficacy endpoints from the study indicated both Ryanodex and Dantrium to be superior to placebo and did not indicate that there was a difference in efficacy between the two treatments; however, the number of animals used in the study was too small to make definitive conclusions in this regard. The similar dantrolene exposures that were observed following identical weight-based doses of Ryanodex and Dantrium support the extrapolation of efficacy findings and dosing recommendations from Dantrium to Ryanodex in humans.

6.1 Indication

The Applicant has proposed the following two indications for Ryanodex, which are quoted from the proposed product labeling:

1.



(b) (4)

6.1.1 Methods

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.2 Demographics

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.3 Subject Disposition

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.4 Analysis of Primary Endpoint(s)

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.6 Other Endpoints

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.7 Subpopulations

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Human studies of the efficacy of Ryanodex were not conducted; therefore, this section is not applicable.

7 Review of Safety

Safety Summary

The safety profile of Ryanodex was characterized utilizing data obtained from both animal and human studies and a review of the postmarketing adverse reactions that have been reported for Dantrium.

While there is a long history of use for dantrolene, Ryanodex, which is estimated to be 150 times more soluble in water than Dantrium, provides the unique opportunity to deliver a bolus dose of dantrolene over a period of several seconds, which contrasts sharply to the minutes it takes to infuse Dantrium. Whether a large bolus of dantrolene poses new safety concerns related to its associated increase in C_{max} was initially evaluated by the Applicant through animal studies designed to determine whether there were risks associated with Ryanodex that were either not observed or were less pronounced with Dantrium. These findings were to be used in the design of subsequent healthy volunteer studies comparing the safety and tolerability of the two products.

The Applicant evaluated the safety of Ryanodex in several types of animal studies. These included:

1. The evaluation of cardiovascular safety of Ryanodex in anesthetized farm pigs (i.e., non-MH susceptible swine)
2. Fourteen-day general toxicology studies of Ryanodex in dogs and minipigs
3. Local tolerance evaluations in rabbits
4. An in vitro evaluation of the hemolytic potential of Ryanodex

The findings of these studies, summarized in Section 7.2.3 below, indicated that there were no new or increased risks associated with Ryanodex treatment compared to Dantrium treatment.

In the healthy human volunteer trials, the Applicant found that the C_{max} for Ryanodex was approximately 40% greater than that for Dantrium, but the AUCs for the two products were the same. The trials also showed that the maximum tolerated dose of Ryanodex in healthy conscious volunteers was 2.5 mg/kg. In the safety database derived from these trials, there were a total of 230 adverse event reported by 51 subjects. A total of 185 of the adverse events occurred after Ryanodex treatment; 34 occurred after Dantrium treatment; 7 occurred after placebo; and 4 occurred prior to administration of study drug. The dose-limiting toxicities (DLT) occurred more frequently with Ryanodex than with Dantrium and consisted of increased incidence and/or intensity of some of the Dantrium-labeled adverse reactions some of which are to be expected based on the mechanism of action of the products. These DLTs included weakness, dysphagia, dizziness, fatigue, somnolence, and nausea. The weakness and dysphagia may be attributable to the muscle relaxant properties of Ryanodex. There

were no serious adverse events for either Ryanodex or Dantrium, and there were no discontinuations.

Analyses of the reported adverse events indicated that 30-second infusions of Ryanodex were more likely to be associated with adverse events and with more severe adverse events than infusions lasting 1 or 5 minutes. The dose of Ryanodex infused over the course of 30 seconds also appeared to affect the incidence of adverse events. The four severe adverse events in the clinical program occurred with the administration of Ryanodex, 1.75 mg/kg or 2 mg/kg, over the course of 30 seconds. Interestingly, the infusion of 1.75 mg/kg of Ryanodex over 5 minutes appeared to have similar incidences of mild and moderate adverse events as the 30-second infusion; however, the 1-minute infusion had a lower incidence rate than both of the others. This likely indicates that the number of subjects evaluated was too small to distinguish safety differences between dosing groups for the same treatment and that care should be taken in making inferences between Ryanodex and Dantrium as only 31 subjects were treated with Dantrium (which had 5 different dosing groups) and 49 subjects were treated with Ryanodex (which had 9 different dosing groups).

It is worth noting that most adverse events began within 3 hours of study drug administration, and no episodes of weakness began after 1 hour of study drug administration. All adverse events resolved within 72 hours.

Based on these findings and taking into consideration the small number of subjects enrolled in the safety studies and the limited range of doses evaluated, there was no indication of a clinically relevant safety concern that occurred with Ryanodex treatment but not with Dantrium treatment. The TEAE data indicated that those adverse events occurring more frequently following Ryanodex compared to Dantrium, could be readily monitored and easily treated or precautions could be taken to minimize their impact on patient safety, e.g., confining patients to bed rest unless assisted to reduce the risk of falls due to muscle weakness.

The review of the postmarketing safety data for Dantrium did not reveal any new safety concerns.

A last point that should be considered in the benefit-risk analysis relates to the time required to reconstitute and administer the two formulations of dantrolene. For Dantrium, 60 mL of sterile water is required to reconstitute a vial containing 20 mg of dantrolene; for Ryanodex, 5 mL of sterile water is required to reconstitute 250 mg of dantrolene. In an MH episode, the minimum dose of dantrolene is 1 mg/kg. For a 70 kg patient, 4 vials of Dantrium will be needed but only a single vial of Ryanodex. If the maximum 10 mg/kg dose of dantrolene is required, 35 vials of Dantrium will be required but only 3 vials of Ryanodex. It has been postulated that providing the full dose of dantrolene over the course of seconds rather than minutes may break the MH episode sooner and possibly reduce morbidity and mortality. There are no data to support that

hypothesis; however, the differences in time required to reconstitute and administer the two formulations may be substantial, possibly 10-20 minutes depending on the dose required. The time saved by using Ryanodex is time that can be spent instituting the multiple supportive measures needed to reduce morbidity and mortality and making the clinical evaluations necessary to guide therapy. In this regard, Ryanodex offers a benefit over Dantrium; the extent of which is not known.

In summary, the safety data indicate that Ryanodex poses no new risks to patients compared to Dantrium, the currently marketed, approved formulation of dantrolene sodium. Ryanodex appears to be associated with a greater frequency of the known adverse reactions to dantrolene than Dantrium; however, these reactions are generally not life-threatening, occur within a few hours after drug administration while patients are still being carefully monitored, are easily detected, can be readily dealt with, and resolve within 72 hours.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A single Phase 1 trial of the pharmacokinetics, safety, and tolerability of Ryanodex, administered to healthy volunteers, was to have constituted the clinical development program for this NDA. The design of the trial was a cooperative effort between the Applicant and the Division. Partway into the trial, the Applicant made substantial protocol changes to refine several of the safety assessments based on preliminary findings. The revised protocol was executed de novo and was treated by the Applicant as a separate trial for the purposes of analyzing the safety data. Both trials are described in detail in section 9.4 of this review. In addition to analyzing the safety data for the trials individually, the Applicant analyzed the integrated safety data.

7.1.2 Categorization of Adverse Events

The MedDRA dictionary, version 15.1, was used to code the adverse events from the two trials. The 230 adverse events were recorded as 107 unique verbatim terms, which were coded into 58 preferred terms. The coding for each of the adverse events was assessed and found to be consistent with a single exception; weakness was coded as either muscular weakness (7 events) or asthenia (19 events). For the purposes of this review, the two preferred terms will be combined under term “muscular weakness.”

There was no evidence that the coding was systematically either too narrow or too broad, i.e., that splitting or lumping of adverse events had occurred.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The data from the two trials were combined to estimate and compare instances of adverse events. While there were differences in the manner and types of data collected, the two trials were sufficiently similar in the doses of Ryanodex studied as well as the timing and types of safety assessments made to allow the data to be combined. Table 3 summarizes the exposures to Ryanodex in the clinical development program.

Table 3. Ryanodex treatments and exposures for the clinical trials

Dose (mg/kg)	Ryanodex Treatments									
	1		1.75			2		2.25	2.5	
Duration of Infusion	30 sec	1 min	30 sec	1 min	5 min	30 sec	1 min	1 min	1 min	
Number of Subjects	4	3	9	4	4	2	4	4	15	

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 46 healthy volunteers were exposed to Ryanodex in the two clinical trials conducted. These included 19 subjects in Trial 1201A and 43 subjects in Trial 1201. Each subject received a single treatment with Ryanodex. The Ryanodex treatments administered in the two trials are summarized in Table 4, Table 5, and Table 6 below.

Table 4. Dosing exposures for Trial 1201A

Dose Ryanodex	30 second infusion (n)	5 minute infusion (n)	Total (n)
1 mg/kg	3 female subjects 1 male subjects	0	4
1.75 mg/kg	3 female 6 male subjects	2 female subjects 2 male subjects	13
2 mg/kg	2 male subjects	0	2
Total	15	4	19

Table 5. Dosing exposures for Part 1 of Trial 1201 (based on Table 2.7.4-2, p. 11 Section 2.7.4 of NDA submission)

Dantrolene Sodium Dose Level	Treatment Groups	
	Ryanodex 1 minute infusion	Dantrium 50 mL/min infusion
1.0 mg/kg	3 male subjects	3 male subjects
1.75 mg/kg	4 male subjects	4 male subjects
2.0 mg/kg	4 male subjects	4 male subjects
2.25 mg/kg	4 male subjects	4 male subjects
2.5 mg/kg	4 male subjects	4 male subjects
Totals	19	19

Table 6. Dosing exposures for Part 2 of Trial 1201

Dantrolene Sodium Dose Level	Ryanodex (1 minute infusion)/ Dantrium (50 mL/min infusion) Crossover*	
	New Enrollees	From Part 1; 2.5 mg/kg dose groups (treated with alternative study drug)
2.5 mg/kg	2 male subjects 6 female subjects	7 male subjects

* One subject treated with Dantrium did not participate in the crossover; therefore, 16 subjects were treated with Dantrium but only 15 subjects were treated with Ryanodex.

Of the 46 subjects enrolled and treated with active study drug, 14 were female. All of these subjects were exposed to Ryanodex; 6 were also exposed to Dantrium in Part 2 of Trial 1201. The main demographic features of the subjects for the two trials are summarized in Table 7 below.

Table 7. Summary demographics of subjects in the clinical trials (active treatments only) derived from the ADSL dataset in the ISS

Parameter	Dose (mg/kg)									
	1		1.75		2		2.25		2.5	
Study Drug	A	B	A	B	A	B	A	B	A	B
Gender										
Male	4	3	12	4	6	4	4	4	9	10
Female	3	0	5	0	0	0	0	0	6	6
Age (years)										
Mean	32	25	27	34	26	31	30	29	30	29
Minimum	19	21	20	26	21	25	25	25	42	42
Maximum	40	28	42	42	30	41	35	33	22	22
Race										
White	4	2	13	3	4	3	2	2	8	9
Black	2	1	2	1	1		2	2	5	5
Other	1		2		1	1			2	2
BMI										
Mean	28	25	27	25	24	23	24	23	24	24
Minimum	20	23	21	22	22	20	20	21	28	28
Maximum	31	29	32	30	29	27	30	25	20	20

A = Ryanodex
 B = Dantrium

As indicated in the table, most of the subjects were young, white, male adults who tended to be overweight. Given the clinical experience with Dantrium and the lack of any evidence to suggest that either safety or efficacy is affected by gender, age, race or body mass index (BMI), the skewed demographics of the subjects in the safety database are not likely to adversely affect the applicability of the risk profile to the overall patient population.

7.2.2 Explorations for Dose Response

In the two clinical trials, as in clinical practice, dantrolene was administered acutely. All subjects received single doses of Ryanodex or the active comparator, Dantrium. At the highest dose in the clinical trials, 2.5 mg/kg, 15 subjects were treated with both Dantrium and Ryanodex as part of the crossover segment of the trial; they were treated

with a single dose of each formulation following a minimum wash-out period of 96 hours. The doses of Ryanodex evaluated in the clinical trials ranged from 1 mg/kg to 2.5 mg/kg as indicated in Table 4, Table 5, and Table 6 above.

It is noteworthy that the Applicant administered Ryanodex doses in three different ways:

1. 30 second infusions
2. 1 minute infusions
3. 5 minute infusions

The adverse events that were classified as severe all occurred with 30 second infusions. There were six such events that occurred in three subjects. Of these, two (generalized weakness) occurred in two subjects treated with 1.75 mg/kg doses; the other four events (hypotension, dizziness, oxygen desaturation and respiratory muscle weakness) occurred in a subject treated with a 2 mg/kg dose.

Of the 90 adverse events, from both trials, which were classified as moderate, 55 occurred with Ryanodex infusions administered over 30 seconds. Based on these adverse events and the markedly decreased frequency of moderate adverse events associated with 5 minute infusions, the Applicant opted to use a 1 minute infusion period in the second trial and is requesting approval for that infusion period.

Table 8 below shows the numbers and severity of TEAEs by treatment dose and infusion method across the two trials. The table indicates that there was not a dose dependence for either the number of TEAEs or their severity for Dantrium treatments. For Ryanodex, there was an increase in the incidence and severity of TEAEs per subject with increasing dose using a 30 second infusion which was not observed with the 1 minute infusions. Interestingly, a comparison of the incidence and severity of TEAEs per subject for the 1.75 mg/kg dose, the only one for which there are data at three infusion rates, the 30 second and 5 minute infusion rates appeared to be less well tolerated than the same dose administered over 1 minute.

Based on these data, it would appear that a 1 minute infusion rate is appropriate. However, it should be noted that the TEAEs occurring in these healthy volunteers were not life threatening and that in the setting of a life-threatening crisis, such as malignant hyperthermia, administering the starting dose of dantrolene at a faster rate would not be inappropriate given the risk profile. In those clinical settings where there is no urgency in administering the product, e.g., prophylactic use and post-MH crisis care, the patients are likely to be awake and would benefit from a slower administration of the product, i.e., over the course of a minute, in an effort to minimize the risk of an adverse reaction and lessen the severity if one should occur.

Table 8. Severity of treatment emergent adverse events by dose and infusion rate of study drug (derived from ADAE dataset)

Treatment	Dose (mg/kg)	infusion method	N	Adverse Event Count		
				Mild	Moderate	Severe
Dantrium	1	50 ml/min (1.7 mg/min)	3	3	0	0
	1.75	50 ml/min (1.7 mg/min)	4	2	1	0
	2	50 ml/min (1.7 mg/min)	4	3	5	0
	2.25	50 ml/min (1.7 mg/min)	4	3	0	0
	2.5	50 ml/min (1.7 mg/min)	16	15	2	0
Placebo		50 ml/min	4	5	2	0
Ryanodex	1	infused in 30 seconds	4	14	8	0
	1.75	infused in 30 seconds	9	38	36	2
	2	infused in 30 seconds	2	3	11	4
	1	Infused over 1 minute	3			
	1.75	infused over 1 minute	4	2	0	0
	2	infused over 1 minute	4	2	2	0
	2.25	infused over 1 minute	4	2	0	0
	2.5	infused over 1 minute	15	24	3	0
	1.75	infused over 5 minutes	4	14	20	0

7.2.3 Special Animal and/or In Vitro Testing

Drs. Adam Wasserman and Jay Chang of the Pharmacology-Toxicology team evaluated the animal studies conducted in support of the application. The studies included the following:

1. Primary Pharmacology Studies: Anesthetized MHS Pietrain Swine
 - a. A pilot intravenous study of two dantrolene formulations in domestic swine susceptible to malignant hyperthermia
 - b. Single intravenous dose range-finding GLP study for evaluation of the efficacy and safety of Dantrolene formulations in the treatment of malignant hyperthermia in susceptible swine
 - c. Single intravenous dose GLP study for evaluation of the efficacy and safety of Dantrium IV in the treatment of malignant hyperthermia in susceptible swine
 - d. Pilot evaluation of the efficacy and safety of Dantrolene in the treatment of malignant hyperthermia in susceptible swine
 - e. Evaluation of the efficacy and safety of Dantrolene in the treatment of malignant hyperthermia in susceptible swine (pivotal efficacy study)
2. Safety Pharmacology Studies: Anesthetized farm pig
 - a. Pilot study of systemic hemodynamics of Ryanodex in farm pigs
 - b. Systemic hemodynamics of Ryanodex in anesthetized farm pigs

3. Pharmacokinetics Study: Beagle Dog
 - a. Collection and bioanalytical analysis of samples for pharmacokinetic analysis of dantrolene sodium suspension (Ryanodex) in male beagle dogs after a single intravenous dose
4. Pharmacokinetics Study: Gottingen minipig
 - a. Single Dose Intravenous Toxicokinetic Study of Dantrolene Sodium suspension for Injection in Gottingen Minipigs
5. Toxicology Studies: Beagle Dog
 - a. A 14-day study of Dantrolene sodium suspension (Ryanodex) by intravenous injection in dogs with a 14-day recovery period
 - b. An administration study of Dantrolene sodium suspension (Ryanodex) by intravenous bolus injection in dogs
6. Toxicology Studies: Gottingen minipig
 - a. Dantrolene sodium suspension: A dose range-finding toxicity study in minipigs
 - b. Dantrolene sodium suspension (Ryanodex): A 2-week toxicity study in minipigs with a 2-week recovery period

The initial Pharmacology Toxicology team review of the 14-day repeat dose toxicity studies in dog and minipig submitted with the opening of the IND suggested a potential for bone marrow suppression caused by Ryanodex based on decreased reticulocyte counts and red blood cell (RBC) parameters (RBC counts, HGB, HCT) observed in treated dogs and pigs when compared to their respective control groups. There were also histopathological findings of decreased bone marrow cellularity in Ryanodex-treated pigs. In light of these safety concerns, the team performed an expanded review to determine whether the nonclinical safety and efficacy studies supported clinical dosing up to the proposed maximum-labelled Ryanodex dose of 10 mg/kg. Based on this expanded review, which focused on the findings above, they determined or noted the following:

1. In dogs, the changes in reticulocyte and RBC parameter levels observed in Ryanodex-treated males at D15 were not considered to be toxicologically different when compared to pre-dose (baseline) levels for their respective groups. Female dogs did not demonstrate significant alterations in RBC parameters or reticulocytes.
2. The histopathological examination of dogs showed myeloid-specific bone marrow hyperplasia, not hypoplasia, in Ryanodex-treated groups. This was considered to be secondary to the degree of injection site reactions, which included suppurative inflammation, seroma, granulation tissue and necrosis, which were worse with Ryanodex than Dantrium, which was worse than the vehicle control treatment. A subsequent 14-day administration study was undertaken to evaluate the effect on local tolerability of saline infusion before and/or after bolus Ryanodex treatment at the equivalent dose (10 mg/kg) of administered Dantrium IV. Although the study did not include hematology or histopathology evaluations, the study showed that both Ryanodex- and Dantrium-treated animals exhibited

mild dermal and perivascular inflammation with similar general severity. Overall, the toxicity was considered minimal, reversible and/or monitorable at the 10 mg/kg dose, the highest dose tested.

3. In minipigs, notable decreases were observed in absolute reticulocyte levels in animals administered Ryanodex when compared to pre-dose (baseline) values. These changes appeared to be attributable to the vehicle as similar decreases were observed in the vehicle-control treatment groups. However, females given 10 mg/kg Dantrium exhibited greater decreases than females given Ryanodex at the same dantrolene dose. None of the changes were statistically significant due perhaps to the high variability in baseline levels and the variability within groups indicated by the large standard deviations.
4. The reticulocyte changes correlated with microscopic findings of minimal to moderate decreased cellularity of the bone marrow, which was observed only in females treated with the high-dose (70 mg/kg) that died prior to scheduled necropsy. These animals also exhibited generalized lymphoid depletion of the thymus and spleen suggestive of a non-specific stress response. No gross or microscopic pathology lesions were noted at doses \leq 30 mg/kg though minimal to moderate local toxicity was noted at the injection sites including hemorrhage, perivascular inflammation, and hypertrophy/hyperplasia of media and intimal layers of vessel receiving injection. These changes were similar with both the Ryanodex and Dantrium treatments. The NOAEL of this study was determined to be 30 mg/kg based on the mortality at the 70 mg/kg Ryanodex dose with evidence of bone marrow suppression, severe stress, yellow discolored organs (assumed to represent high levels of dantrolene) and thrombi containing brilliant yellow-brown crystals in one animal which also had findings indicative of adverse renal function.
5. In the minipig efficacy study, reticulocyte levels were increased at 1 hour post-administration of Ryanodex, Dantrium, and saline, presumably due to the malignant hyperthermia episode. Saline-treated animals exhibited the highest increase while Ryanodex and Dantrium treatments exhibited similar changes suggesting that dantrolene may have suppressed MH-induced elevations in this parameter. The microscopic evaluations did not include examination of bone marrow in this study

The team determined the safety margins for the 10 mg/kg Ryanodex dose based on AUC and C_{max} using the NOAEL-associated nonclinical toxicokinetic values from the minipig study and the available human PK data. They noted that it is important to keep in perspective that minipigs were dosed daily for 14 consecutive days while dosing in the clinical setting is acute. Based on these data, they found that:

1. The C_{max} and AUC values associated with the minipig NOAEL provide a 7-fold and 3-fold safety margin, respectively, when compared to the mean clinical PK values from subjects administered 2.5 mg/kg Ryanodex.
2. Human PK values for the proposed maximum recommended daily dose of dantrolene, i.e., 10 mg/kg, were predicted based on linear progression of data

from humans given Ryanodex at doses from 1 to 2.5 mg/kg. Compared to the predicted AUC value for a clinical dose of 10 mg/kg, the AUC associated with the minipig NOAEL provides an approximate 0.7-fold exposure margin. However, the AUCs after administration of Ryanodex and Dantrium at all doses tested in both animals and humans were comparable for the two treatments. Given the Agency's previous finding of safety for Dantrium doses of 10 mg/kg, there is no reason to expect an increased risk with a similar dose of Ryanodex.

3. In contrast to the AUC findings, the Ryanodex C_{max} values were typically 40%-50% higher than those of Dantrium at equivalent dose levels in both animals and humans. This finding raised a concern for possible safety issues related to C_{max} ; however, the C_{max} associated with the minipig NOAEL provides a 1.3- to 1.6-fold exposure and safety margin compared to the predicted human C_{max} at 10 mg/kg.

In summary, the animal safety and efficacy studies supported the safety of human dosing with Ryanodex up to the maximum recommended dose of 10 mg/kg based on adequate safety margins from the minipig toxicity study. The dog toxicity study and minipig efficacy study demonstrated comparable toxicity profiles for Ryanodex and Dantrium.

7.2.4 Routine Clinical Testing

The Applicant performed the following clinical evaluations of subjects during the two clinical trials:

- Electrocardiogram
- Oxygen Saturation
- Spirometry
- End tidal CO_2 (et CO_2)
- Maximum inspiratory and expiratory pressures (MIP and MEP, respectively)
- Clinical Laboratory Assessments:
 - i. biochemistry profile
 - ii. complete blood count with differential
 - iii. urinalysis
 - iv. coagulation profile
- Assessments of Subjects' strength including:
 - i. Head Lift
 - ii. Grip Strength
 - iii. Stair Climb

As the nonclinical studies did not identify specific safety concerns that required assessments in humans, the available safety data from Dantrium do not and the TEAE data did not suggest any safety concerns other than the expected effects from antagonizing ryanodine receptors, the clinical assessments made in the two trials were

both appropriate and adequate to characterize the risk profile for the purposes of labeling the product and performing a benefit risk analysis to render a regulatory decision.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant did not conduct any studies to evaluate the metabolism or clearance of Ryanodex or to examine possible drug-drug interactions. (b) (4)

[REDACTED] based on the similarities between Ryanodex and Dantrium for their indications, dosing, systemic exposures, and acute use, it is not expected, and there was no animal or human evidence to suggest there is, a difference between the two products for any of these characteristics.

The Dantrium label provides the following information regarding the metabolism of dantrolene:

Specific metabolic pathways for the degradation and elimination of Dantrium in humans have been established. Dantrolene is found in measurable amounts in blood and urine. Its major metabolites in body fluids are 5-hydroxy dantrolene and an acetylamino metabolite of dantrolene. Another metabolite with an unknown structure appears related to the latter. Dantrium may also undergo hydrolysis and subsequent oxidation forming nitrophenylfuroic acid.

The Dantrium label provides the following information regarding the clearance of dantrolene:

The mean biologic half-life of Dantrium after intravenous administration is variable, between 4 to 8 hours under most experimental conditions. Based on assays of whole blood and plasma, slightly greater amounts of dantrolene are associated with red blood cells than with the plasma fraction of blood. Significant amounts of dantrolene are bound to plasma proteins, mostly albumin, and this binding is readily reversible.

[REDACTED] (b) (4)

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Dantrium is the only approved ryanodine-receptor-antagonist drug product. Intravenous Dantrium was used as the active comparator in Trial 1201 allowing a direct comparison of the adverse event profiles for the two products up to a dose of 2.5 mg/kg. The findings from that trial are described in Section 7.3 below.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported for either of the clinical trials conducted.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events reported for either of the clinical studies conducted.

7.3.3 Dropouts and/or Discontinuations

There were no dropouts or discontinuations in either of the clinical trials conducted.

7.3.4 Significant Adverse Events

The Applicant reported no severe adverse events for any of the subjects treated in the second clinical trial, which went to completion. Those adverse events that did occur in that trial were classified as either mild or moderate and were reported to have resolved without sequelae. The Applicant reported that there were no Grade 3 or 4 adverse events based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0) criteria. They also stated the following regarding significant adverse events:

1. No respiratory failure as defined by ABG results occurred.
2. No hepatic or renal changes that posed a danger to subjects' well-being were observed during the study.
3. There were no clinically meaningful changes from baseline in vital signs or ECG assessments during the study.
4. There were no dose-limiting toxicities.

For this review, of the safety data from the two clinical trials combined were considered taking into account the different infusion rates for the various doses of Ryanodex. In this database, there were six TEAEs, from Trial 1201A, that were classified as severe; all occurred with 30 second infusions of Ryanodex. These events occurred in three subjects. Two of the events (both incidents of generalized weakness) occurred in two subjects treated with a 1.75 mg/kg dose; the other four events (hypotension, dizziness, oxygen desaturation and respiratory muscle weakness) occurred in a subject treated with a 2 mg/kg dose.

Of the 90 adverse events, from both trials, which were classified as moderate, 80 were related to administration of Ryanodex, and 55 occurred with Ryanodex infusions administered over 30 seconds, indicating the rate of infusion is likely to play a role in determining the intensity of the adverse reaction. The moderate TEAEs occurring with Ryanodex treatments were categorized with 19 preferred terms. The four most frequently reported TEAEs were dizziness (12 events), somnolence (11 events) asthenia (10 events), and fatigue (9 events); all of which are listed as adverse reactions in the Dantrium label.

There were no significant adverse events meeting the ICH E3 definitions of marked hematological and other laboratory abnormalities, and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

7.3.5 Submission Specific Primary Safety Concerns

Safety concerns for this submission were based on two considerations: the known risks associated with dantrolene based on the clinical experience with intravenous Dantrium, and the unknown risks associated with a bolus dose of dantrolene and the effects the high concentrations of the product might have as it passes through the major organs before it is diluted to levels observed with exposures to Dantrium.

The known risks associated with intravenous dantrolene, as described in the Dantrium label include the following (from the Adverse Reaction and Overdosage sections of the label):

1. Skeletal muscle weakness, including possible respiratory depression
2. Lightheadedness
3. Difficulty swallowing and choking
4. Fatal and non-fatal liver disorders of an idiosyncratic or hypersensitivity type
5. Pulmonary edema developing during the treatment of malignant hyperthermia crisis in which the diluent volume and mannitol needed to deliver dantrolene possibly contributed
6. Thrombophlebitis
7. Urticaria and erythema
8. Anaphylaxis.
9. Alterations in the state of consciousness (e.g., lethargy, coma)
10. Vomiting,
11. Diarrhea
12. Crystalluria

The Applicant did not formally compare the two products for these specific adverse events; however, there were no adverse events for either product related to pulmonary edema, thrombophlebitis, urticaria, erythema (at the injection site) or anaphylaxis.

Table 9 below compares the incidence of the other known risks by the treatment groups.

Table 9. Incidents of treatment-emergent adverse events similar to those reported in the Adverse Reactions and Overdosage sections of the Dantrium label

Adverse Event Preferred Term	Dantrium n=31	Placebo n=4	Ryanodex n=49
Asthenia	0	0	19
Asthenopia	1	0	0
Confusional state	0	0	2
Dizziness	0	1	17
Dysphagia	4	0	11
Dyspnoea	0	0	8
Fatigue	1	0	14
Feeling abnormal	3	0	3
Feeling drunk	0	0	1
Flushing	1	0	9
Inspiratory capacity decreased	0	0	2
Muscular weakness	2	0	5
Nausea	3	1	11
Neutropenia	1	0	0
Oxygen saturation decreased	0	0	1
Respiratory muscle weakness	0	0	1
Somnolence	4	0	15
Vomiting	2	0	1

The table indicates that Ryanodex treatment is associated with the same types of adverse events as are described in the Dantrium label, but these events occur more frequently with Ryanodex treatment. The differences in the incidences for these events may be due to the greater C_{max} for dantrolene that occurs with Ryanodex treatment. Regardless of the reason for the differences, it should be noted that the events themselves were not generally life threatening, could be readily monitored, and resolved spontaneously. The events that pose the greatest risk to patients' safety are those related to diminished ventilatory capacity. In the clinical setting where Ryanodex will be used, patients will often be intubated and mechanically ventilated when the product is administered and continue to be so until the malignant hyperthermia crisis has ended. In addition, patients will be monitored for adequacy of respiration for a period of time following the crisis in the PACU or ICU setting, depending on the severity of the crisis. Overall, the duration of monitoring will exceed the duration of the respiratory related adverse events.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 230 adverse events were reported for the two clinical trials; all of which occurred following administration of study drug. Of these adverse events, 160 occurred in the initial trial (EGL-Dantrolene-1201a) and 70 occurred in the second trial (EGL-Dantrolene-1201). A total of 51 of the subjects experienced treatment-emergent adverse events (TEAEs).

The Applicant did not provide a table of adverse events for either the individual trials or the integrated dataset. Table 10 was generated from the adverse event database combining the events for each study drug regardless of the dose and method of administration (infusion or bolus) and includes only the TEAEs which were reported for the Ryanodex treated subjects. The number of exposures for each treatment arm takes into account that 15 subject were treated a second time in Period 2 of trial 1201, i.e., these were the subjects that received a 2.5 mg/kg dose of Ryanodex or Dantrium during Period 1 and where then given a 2.5 mg/kg dose of the alternative treatment following a washout period. Thus the total number of exposures is 84 for the 69 subjects enrolled in the two trials.

The data in Table 10 indicate that, overall, the incidence of TEAEs was greater for Ryanodex than Dantrium.

Table 10. Summary of treatment-emergent adverse events in decreasing frequency for Ryanodex

System Organ Class	Preferred Term	Ryanodex N=49	Dantrium N=31	Placebo N=4
		n (%)	n (%)	n (%)
Nervous system disorders	Dizziness	17 (35)	0 (0)	1 (25)
	Somnolence	15 (31)	4 (13)	0 (0)
	Dysarthria	6 (12)	0 (0)	0 (0)
	Headache	2 (4)	4 (13)	0 (0)
	Muscle contractions involuntary	2 (4)	0 (0)	0 (0)
	Paresthesia	2 (4)	0 (0)	1 (25)
	Dysgeusia	1 (2)	1 (3)	0 (0)
	Head discomfort	1 (2)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	Muscular weakness	21 (43)	1 (3)	0 (0)
	Pain in extremity	2 (4)	1 (3)	0 (0)
	Back pain	1 (2)	1 (3)	0 (0)
	Muscle spasms	1 (2)	0 (0)	0 (0)
	Musculoskeletal chest pain	1 (2)	1 (3)	0 (0)
	Myalgia	1 (2)	0 (0)	0 (0)
	Sensation of heaviness	1 (2)	0 (0)	0 (0)

System Organ Class	Preferred Term	Ryanodex N=49	Dantrium N=31	Placebo N=4
		n (%)	n (%)	n (%)
General disorders and administration site conditions	Fatigue	13 (27)	1 (3)	0 (0)
	Feeling hot	4 (8)	0 (0)	0 (0)
	Infusion site pain	3 (6)	0 (0)	0 (0)
	Feeling abnormal	3 (6)	3 (10)	0 (0)
	Chills	1 (2)	0 (0)	0 (0)
	Feeling drunk	1 (2)	0 (0)	0 (0)
Gastrointestinal disorders	Dysphagia	11 (22)	4 (13)	0 (0)
	Nausea	11 (22)	3 (10)	1 (25)
	Abdominal pain	1 (2)	0 (0)	0 (0)
	Vomiting	1 (2)	2 (6)	0 (0)
Respiratory, thoracic and mediastinal disorders	Dyspnea	8 (16)	0 (0)	0 (0)
	Dysphonia	4 (8)	1 (3)	0 (0)
	Respiratory muscle weakness	1 (2)	0 (0)	0 (0)
Cardiac disorders	Palpitations	3 (6)	0 (0)	0 (0)
	Sinus tachycardia	2 (4)	0 (0)	0 (0)
	Tachycardia	2 (4)	0 (0)	0 (0)
	Atrioventricular block	1 (2)	0 (0)	0 (0)
	Bradycardia	1 (2)	0 (0)	0 (0)
	Nodal arrhythmia	1 (2)	0 (0)	0 (0)
Psychiatric disorders	Euphoric mood	4 (8)	0 (0)	0 (0)
	Anxiety	2 (4)	0 (0)	0 (0)
	Confusional state	2 (4)	0 (0)	0 (0)
	Bradycardia	1 (2)	0 (0)	0 (0)
	Nodal arrhythmia	1 (2)	0 (0)	0 (0)
Vascular disorders	Flushing	9 (18)	1 (3)	0 (0)
	Hypotension	1 (2)	0 (0)	0 (0)
Eye disorders	Diplopia	2 (4)	0 (0)	0 (0)
	Vision blurred	5 (10)	1 (3)	0 (0)
Investigations	Inspiratory capacity decreased	2 (4)	0 (0)	0 (0)
	Oxygen saturation decreased	1 (2)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	Hyperhidrosis	2 (4)	0 (0)	0 (0)
Renal and urinary disorders	Chromaturia	1 (2)	0 (0)	0 (0)
Ear and labyrinth disorders	Ear discomfort	1 (2)	0 (0)	0 (0)

The differences between Ryanodex and Dantrium are noteworthy in two ways.

First, most of the differences pose no increase in risk to subjects due to their short duration as well as the level of monitoring and the level of activity for patients when treated with the product. For those TEAEs that suggest a risk to patient safety, e.g.,

dyspnea, respiratory muscle weakness and oxygen saturation decreases, the events were mild and limited in duration to the extent that no apparent change in respiratory function occurred, i.e., there were no oxygen saturations <95%, supplemental oxygen and airway manipulations were not required, and arterial blood gas parameters were not abnormal. For the other risks, e.g., muscle weakness, dizziness, and somnolence, the risk to the patients are low when the drug is used to treat an MH crisis as the patient is under anesthesia and confined to the operating room table. In addition, the duration of these events is also relatively short, on the order of a couple hours such that most will have subsided before the patient is conscious and permitted to ambulate.

Second, while the difference in TEAEs between the products is not expected to pose an increase risk to patients who are being treated for an MH crisis, there is the concern that the differences may pose a risk to patients treated with the product prophylactically prior to their anesthetic. These patients are generally awake, or at only slightly sedated, and may be permitted to ambulate, e.g., allowed to use the lavatory facilities. For these patients, it will be important that they and the clinical staff be informed of the possible reactions, confined to bed rest following administration of the product, and monitored for the possible need of intervention, e.g., treatment of nausea. As the possible reactions to Ryanodex for these patients are relatively short in duration, easily monitored, and readily treated if necessary, the use of Ryanodex for prophylaxis does not pose a substantial enough increase in risk that it should not be used for this indication; however, the difference between Ryanodex and Dantrium are significant enough that the label should inform clinicians of the differences between the two products and the need for more careful monitoring and for confinement of patients to bed rest, unless assisted by staff, following its administration for prophylaxis against an MH crisis.

7.4.2 Laboratory Findings

The Applicant performed the following analyses for the clinical laboratory evaluations: changes from baseline by treatment and dose groups and shifts in values from baseline by treatment group.

They reported the following findings for the clinical chemistry evaluations:

1. There was a decrease in creatine phosphokinase (CPK), at 24 and 72 hours post dose, which was consistent across the Ryanodex and Dantrium dose and treatment groups, as well as observed in the placebo group. This decline was expected given the pharmacological action of dantrolene sodium (a skeletal muscle relaxant) and the lack of activity while confined in the CRU.
2. There was a shift in calcium from normal to low at 24 hours (3 subjects, 6%) and at 72 hours (3 subjects 6%) post-Ryanodex dose, and a shift from normal to high in phosphorous 24 hours post-dose in both the Ryanodex (5 subjects, 10%) and Dantrium (4 subjects, 13%) treatment groups.

3. Changes in chemistry laboratory values were analyzed by gender across all treatment groups, and in the 2.5 mg/kg crossover-dose treatment group. A decrease in CPK values was observed in both the male and female Ryanodex and Dantrium treatment groups; however, no gender specific changes were observed.

The following findings were reported for the clinical hematology evaluations:

1. No clinically relevant consistent changes from baseline were observed in any hematology parameters and no dose effects were observed.
2. There was a shift in hematocrit from normal to low at 24 hours (3 subjects, 6%) and 72 hours (6 subjects, 12%) post dose, a shift in hemoglobin from normal to low at 24 hours (2 subjects, 4%) and 72 hours (5 subjects, 10%) post dose, red blood cell count (RBC) from normal to low at 24 hours (4 subjects, 8%) and 72 hours (5 subjects, 10%) post dose in the Ryanodex treatment group.
3. Similar shifts in hematocrit, hemoglobin, and RBC from normal to low were observed in the Dantrium dose groups.
4. Changes in hematology laboratory values were analyzed by gender across all treatment groups and in the 2.5 mg/kg crossover-dose treatment group. There were no clinically relevant changes from baseline and no gender effects (overall or in the 2.5 mg/kg dose group between genders) observed.

For clinical coagulation parameter assessments, the Applicant reported the following findings:

1. There was a shift from normal to high in international normalized ratio (INR) values in 2 subjects (4%) in the Ryanodex treatment group 24 hours post dose and in 3 subjects (6%) 72 hours post dose.
2. There was a shift in Prothrombin time (PT) values from normal to high in 2 subjects (4%) in in the Ryanodex treatment group 24 hours post dosing and in 3 subjects (6%) 72 hours post dosing.
3. Overall, coagulation values were normal at baseline and there were no clinically significant shifts in values during the study period.
4. Changes in coagulation values were analyzed by gender across all treatment groups and in the 2.5 mg/kg crossover-dose treatment group. Overall, there were no clinically significant changes in coagulation values from baseline between genders or in the 2.5 mg/kg dose group between genders.

For the results of the urinalysis data, the Applicant reported the following:

Overall, no clinically significant changes in urinalysis laboratory values were observed in this study.

1. No changes in urinalysis values from baseline were observed between males and females in either treatment group or between genders in the Ryanodex 2.5mg/kg dose group.
2. There was a comparable shift from baseline to abnormal in appearance and color in both the Ryanodex and Dantrium treatment groups.

3. There were 6 (12%) Ryanodex subjects that showed abnormal protein levels 72 hours post dose in comparison to 8 (26%) subjects in the Dantrium group.

A summary of new or worsening clinical laboratory abnormalities based on National Cancer Institute- Common Terminology Criteria for Adverse Events (NCICTCAE) was analyzed by treatment group and dose. The overall incidence of changes in clinical laboratory values was similar between the Ryanodex and Dantrium treatment groups. Subjects treated with Ryanodex demonstrated an increase in sodium, coagulation/international normalized ratio (INR), and platelet count and an increase in white blood cell (WBC) count, although the Dantrium group had a greater number of subjects with an increase in WBC. The Ryanodex 1.0 mg/kg dose group had a greater number of subjects with abnormalities in INR (2/7, 28%) in comparison to the Dantrium group (0/3). The Ryanodex 1.75 mg/kg dose group subjects exhibited alterations in multiple laboratory values including magnesium, sodium, INR, neutrophils, platelet count, and WBC count, which corresponded to the higher incidence of AEs observed in this dose group. The Ryanodex and Dantrium groups had a comparable number of subjects with abnormalities in white blood cell count and neutrophils at the 2.25 and 2.5 mg/kg doses. The Ryanodex group also had more subjects (2/4, 50%) with alterations in sodium values in comparison to the Dantrium group (0/4). It was noted that despite these differences for the two treatment groups, no laboratory finding reached the level that it was considered an adverse event according to National Cancer Institute- Common Terminology Criteria for Adverse Events (NCICTCAE) criteria. Therefore, a formal outlier analysis was not conducted by the Applicant.

Based on their analyses, the Applicant drew the following conclusions for the effect of Ryanodex on clinical laboratory parameters:

1. The overall incidence in changes in clinical laboratory values was similar between the Ryanodex and Dantrium groups, although subjects treated with Ryanodex demonstrated abnormalities in sodium, coagulation/INR, and platelet count and a higher number of Dantrium-treated subjects demonstrated abnormalities in WBC count.
2. Alterations in laboratory values that were observed with Ryanodex treatment were frequently observed in the Dantrium treatment group as well.
3. There was decrease in creatine phosphokinase (CPK), at 24 and 72 hours post dose, which was comparable in the Ryanodex and Dantrium dose and treatment groups, and also observed in the placebo group. This decline was expected given the pharmacological action of dantrolene sodium (a skeletal muscle relaxant) and the lack of activity while confined in the clinical research unit.

To verify the Applicant's conclusions, the laboratory parameters evaluated in the two trials were examined for values outside the normal range and clinically significant shifts from baseline. Special attention was paid to the liver and renal function profiles. The findings are summarized below:

1. There were 32 measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin that were outside the normal limits for the laboratory making the assessment. All of these were values above the upper limit of normal, and 20 of these measurements were screening or baseline (pre-study drug) values.
2. There were no values of AST that exceeded the normal limits.
3. There were 5 values of ALT that were above the upper limit of normal (60 U/L). The highest of these was 69 U/L, which was actually a decrease from the elevated (89 U/L) baseline value.
4. For total bilirubin, there were 7 measurements above the upper limit of normal (1.4 mg/dL). The greatest of these occurred after Dantrium (2.5 mg/kg) treatment with a value of 2.5 mg/dL, which was up from the baseline value of 0.9 mg/dL. For Ryanodex, there was an increase to 2.3 mg/dL from 1.7 mg/dL that was observed after a 2.5 mg/kg dose.
5. There were no systematic shifts from baseline or elevations above normal limits that occurred with either Dantrium or Ryanodex treatment or increasing doses of either product.
6. There were 14 values of blood urea nitrogen (BUN) or creatinine that were outside the range of normal limits for the processing laboratory. These included 8 values measured at screening or baseline.
7. For creatinine, there was a single increase from baseline to above the upper limit of normal (1.5 mg/dL). That occurred with Dantrium treatment (2.5 mg/kg) and consisted of an increase from 1.42 mg/dL to 1.52 mg/dL. There was a single post-treatment measure of creatinine that was below the lower limit of normal (0.7 mg/dL); however, this measure, 0.69 mg/dL, represented a return toward normal levels compared to the baseline value of 0.67 mg/dL, which occurred following treatment with Ryanodex 2 mg/kg.
8. As with liver function, there were no systematic shifts from baseline or outliers from normal limits for renal function that occurred with either Dantrium or Ryanodex treatment or increasing doses of either product.
9. There were no clinically relevant systematic shifts from baseline or outliers from normal limits found with either Ryanodex or Dantrium treatments, at any of the doses for the electrolytes, glucose, hematology and coagulation parameters, and urinalysis parameters tested.

In summary, there were several minor but clinically insignificant changes in clinical laboratory parameter associated with the use of both Ryanodex and Dantrium. There was no evidence that either product had any dose-dependent effect on these measures or that one of the products had a greater effect than the other on any parameter.

7.4.3 Vital Signs

The Applicant stated that there were no clinically meaningful changes from baseline in any of the vital sign assessments during the study.

Vital signs including diastolic and systolic blood pressure, pulse oximeter oxygen saturation pulse rate, respiratory rate, and temperature, were measured at baseline and throughout the study up to 72 hours following study drug administration. Manual BP measurements taken at the (b) (4) site were compared with arterial BP (or compared to manual BP measurements when the arterial line was not present) taken at the CCD site in Part 1 of the study. Changes in vital signs were analyzed by gender across all treatment groups and in the 2.5 mg/kg dose treatment group. The Applicant reported the following findings:

1. There was a general increase in diastolic blood pressure across all doses for the first 2 to 3 hours in the Ryanodex and Dantrium treatment groups.
2. The effect was consistent between genders.
3. There was a general increase in systolic blood pressure for the first 2 hours in post both Ryanodex and Dantrium dosing, however no consistent effects of dose or gender were observed.
4. There was a general increase in pulse rate across all dose groups for up to 8 hours after dosing in both the Ryanodex and Dantrium treatment groups with a trend towards a larger increase in males; however, this increase did not reach the level to be classified as clinically relevant or an adverse event.
5. There was a trend towards an increase in respiration rate lasting for approximately 15 minutes post dosing; this effect seemed to be more limited to the 2.0 and 2.5 mg/kg Ryanodex doses. The increases were not deemed to be clinically relevant by the primary investigator and the changes did not reach a difference that was classified as clinically relevant or as an adverse event.

Shifts in vital signs from baseline were analyzed by treatment group. There was a shift in pulse rate from normal to abnormal (abnormal: absolute value < 45 or >101 bpm) 1 minute post Ryanodex dosing in 4 subjects (8%). There were a number of shifts in respiratory rate post Ryanodex dosing from normal to abnormal (abnormal: absolute value > 17 breaths/min) beginning from 1 minute post dose (11 subjects, 22%) out to 24 hours post dose (8 subjects, 16%). This shift from normal to abnormal respiratory rate was also observed to a lesser extent in the Dantrium treatment group.

There was a shift in systolic blood pressure from normal to abnormal (abnormal: ≤ 89 or > 141 mmHg) beginning from 1 minute post dose (11 subjects, 22%) and continuing until 8 hours post dose in the Ryanodex treatment group. A similar shift in systolic blood pressure from normal to abnormal was observed in the Dantrium treatment group, although to a lesser extent beginning at 1 minute post dose (8 subjects, 26%).

The Applicant concluded that, overall, there were no clinically significant changes in diastolic or systolic blood pressure, pulse, or respiratory rate values.

The vital signs datasets were evaluated to confirm the Applicant's findings. The results of these evaluations are described below.

Systolic blood pressures (SBP) were measured 1,655 times during the two trials. There were 123 instances for which the Applicant reported blood pressure measurements as "not done." In all, there were 77 measurements that were >140 mmHg; among these were 7 incidents of systolic blood pressure greater than 160 mmHg. Most of the elevated pressures were recorded within the first hour of study drug administration and were of similar proportions for both the Dantrium and Ryanodex treatment groups. Most instances were associated with the 2 mg/kg doses and higher. Systolic hypotension, i.e., SBP <100 mmHg, was noted with 170 of the measurements; 12 cases of which occurred pre-dose. Of these 170 incidents, there were 21 that were less than 90 mmHg, most of which were related to higher doses (>1.75 mg/kg) of Ryanodex or the 30-second injections of 1.75 mg/kg doses of Ryanodex. For three subjects, the hypotension occurred during both parts of the crossover study, i.e., following 2.5 mg/kg of Dantrium and 2.5 mg/kg of Ryanodex. Hypotension associated with SBP \geq 90 mmHg was evenly distributed between the treatment groups and generally occurred between 3 and 48 hours post-dose.

In summary, both Dantrium and Ryanodex were associated intermittent decreases in SBP that was observed up to 48 hours post-dosing and with intermittent increases in systolic blood pressure during the first hour following administration. The decreases in SBP occurred more often and appeared to be related to dose and rate of administration; however, it occurred with both Ryanodex and Dantrium treatments, and did not appear to pose a greater risk with one treatment over the other. Similarly, the increases in SBP were relatively small, and in the general population, would not likely be associated with increased morbidity.

Diastolic blood pressures (DBP) were measured 1,778 times during the two trials. There were 123 instances for which the Applicant reported blood pressure measurements as "not done." The measurements ranged from 55 mmHg to 99 mmHg. There were 17 values >90 mmHg. Of these, 4 occurred prior to study drug administration; 1 was associated with placebo treatment; 6 were associated with Dantrium treatment and 6 were associated with Ryanodex treatments; none occurred with the highest dose (2.5 mg/kg) of Ryanodex. There were 116 instances of DBP < 70 mmHg; 15 of which occurred prior to treatment with study drug. Of the instances occurring after study drug administration, 44 were associated with Dantrium treatment; 62 were associated with Ryanodex treatment. Thirteen of the instances associated with Ryanodex treatment occurred in 2 subjects treated with the 2.5 mg/kg dose with all but one instance occurring at least an hour after the Ryanodex was administered; neither of these subjects experienced an adverse event.

In summary, both Dantrium and Ryanodex were associated intermittent increases and decreases in diastolic blood pressure with more instances of decreases than increases.

The decreases occurred at various time points following study drug administration ranging from minutes to day; whereas, the increase tended to occur within a couple hours of dosing. Overall, the changes in DBP were, from a clinical perspective, relatively small, similar for Ryanodex and Dantrium, and did not appear to pose a greater risk with one treatment over the other.

Pulse rates were measured 1,656 times; there were 123 instances where the measurements were listed as “not done.” There were 14 instances of tachycardia, i.e., pulse \geq 100 bpm, only two of which involved heart rates greater than 110 bpm; both occurred in the same subject and were measured at 1 minute post-Ryanodex 1.75 mg/kg 30 second infusion (111 bpm) and at 72 hours post dose (138 bpm). There was no apparent association between Ryanodex treatment and tachycardia. Similarly, there were 286 instances of bradycardia, i.e., pulse \leq 60 bpm. Of these, 22 measurements were less than 50 bpm, but none were less than 46 bpm. Many of the instances of bradycardia occurred during screening; the others occurred at varying times following treatment with either Ryanodex or Dantrium. There was no apparent association between Ryanodex treatment and bradycardia.

Oxygen saturation was measured 1,853 times; there were 4 measurements that were listed as “not done.” All but five of the measurements were above 90%. Of the measurements less than 90%, four occurred following treatment with Dantrium; one occurred following treatment with Ryanodex 2 mg/kg injected over 30 seconds. There was no apparent association between Ryanodex treatment and oxygen desaturation.

Respiratory rate was measured 1437 times; there were 322 measurements that were listed as “not done.” There were two instances of respiratory rates less than 10 bpm; one report each for 8 and 9 bpm. There were 44 incidents of respiratory rates greater than 20 bpm; the highest were two reports of rates of 26 bpm. There was no apparent association between Ryanodex treatment and respiratory rate.

In conclusion, the vital sign data do not indicate either a clinically relevant change from baseline with Ryanodex treatment or a clinically relevant difference between treatment with Ryanodex and Dantrium.

7.4.4 Electrocardiograms (ECGs)

Baseline ECG values and changes from baseline by treatment group and dose groups were evaluated by the Applicant. They found that there was a slight decrease in QT interval and QTc interval at 15 minutes and 1 hour post dosing which was similar across all Ryanodex dose groups. Shifts in ECG values from baseline were analyzed by treatment group were also evaluated. The findings reported included:

1. ECG values were normal at baseline and the majority of values did not shift during the study period.

2. There was a shift in heart rate from normal to low at Day 4 in both the Ryanodex and Dantrium treatment groups (3 subjects in each group; 6% of the Ryanodex group and 10% of the Dantrium group).
3. A shift in the PR interval from normal to high occurred in the Ryanodex treatment group (3 subjects, 6%) at Day 1, 15 minutes post treatment and 1 hour post-dose (3 subjects, 6%).

Changes in ECG results were analyzed by gender across all treatment groups and in the 2.5 mg/kg dose treatment group. The Applicant reported that, overall, there were no clinically significant changes in ECG values from baseline in the 2.5 mg/kg dose group between genders.

The ECG data were analyzed to evaluate whether there were any systematic changes from baseline that occurred with either Ryanodex or Dantrium treatments or that appeared to be dose dependent for either treatment. For PR intervals, QTcF, QRS intervals, and heart rate, no clinically relevant differences were found supporting the Applicant's conclusions Ryanodex does not affect the electrocardiogram in a clinically meaningful way and is not distinguishable from Dantrium in this regard.

7.4.5 Arterial Blood Gas (ABG)

Routine arterial blood gas (ABG) measurements were made only at the CCD site, i.e., Study 1201. The Applicant reported the following findings for these measurements:

1. Overall there were no significant changes in ABG.
2. No respiratory failure, as defined by ABG results, occurred.
3. Shifts in ABG values from baseline were analyzed by treatment group. The ABG values were normal at baseline, and the majority of values did not shift during the study period.
4. There was a shift in SaO₂ values from normal to high at 20 minutes post-dosing in 3 subjects (13%), and a shift in PaCO₂ from normal to low at 5 minutes post-dose (4 subjects, 17%), 20 minutes post-dose (4 subjects, 17%), and 1 hour post-dose (4 subjects, 17%) in the Ryanodex treatment group.

An analysis of the data provided indicated that neither treatment had any impact on ABG parameters and that the Applicant's conclusions are justified.

7.4.6 Special Safety Studies/Clinical Trials

No special safety studies were required or conducted in support of this application.

7.4.6 Immunogenicity

The Applicant did not make any assessments of the immunogenic potential of Ryanodex. No immunogenicity issues related to the use of Ryanodex were identified during the nonclinical and the clinical development programs. Immunogenic responses related to the use of Dantrium have not been reported.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The numbers of subjects evaluated were small for each of the different treatment groups; however, the Applicant noted that there was no dose-dependent increase in specific adverse events. They provided a summary of adverse events by treatment (Table 11 below) which indicates there was no overall increase in treatment emergent adverse events (TEAEs) with increasing dose of either Ryanodex or Dantrium and there is no clinically meaningful difference between Ryanodex and Dantrium at any given dose. It is important to note that the number of subjects is small both within each treatment group and for the safety database as a whole.

Table 11. Adverse event counts by treatment and dose (based on Table 5, p. 12 of Integrated Clinical Safety Data Assessment)

Dose	1.0 mg/kg		1.75 mg/kg		2.0 mg/kg		2.25 mg/kg		2.5 mg/kg		Pla- cebo
	A (N=7)	B (N=3)	A (N=17)	B (N=4)	A (N=6)	B (N=4)	A (N=4)	B (N=4)	A (N=15)	B (N=16)	
Number of subjects with at least 1 TEAE	4 (57%)	2 (67%)	15 (88%)	3 (75%)	4 (67%)	2 (50%)	2 (50%)	3 (75%)	11 (73%)	9 (56%)	2 (50%)
Number of subjects with TEAEs related to Study Drug ^A	4 (57%)	2 (67%)	15 (88%)	3 (75%)	4 (67%)	2 (50%)	2 (50%)	3 (75%)	9 (60%)	7 (44%)	2 (50%)

^A Related adverse events are categorized as “Probably Related” and “Definitely Related.”

TEAE = treatment-emergent adverse event

A = Ryanodex treatment

B = Dantrium treatment

In Table 12 below, the TEAE counts for each system organ class (SOC) are listed for Ryanodex and Dantrium. Excluded from this table were the following SOCs for which there was a single TEAE across all treatment groups:

- Blood and lymphatic system disorders
- Ear and labyrinth disorders
- Infections and infestations
- Renal and urinary

In addition to the above, the SOCs Investigations and Skin and subcutaneous tissue disorders were not included as these SOC each included only three and two TEAES, respectively, across all treatment groups with none occurring at a dose greater than 2 mg/kg.

The table suggests that there were no dose-dependent TEAEs for any of the SOCs for subjects treated with either Ryanodex or Dantrium. To assess the possibility that specific TEAEs observed at the higher doses of dantrolene were not observed with similar frequency at lower doses, the TEAEs reported at doses of 2.5 mg/kg were evaluated. Flushing and “feeling abnormal” were the only two TEAEs that occurred more frequently with higher doses of Ryanodex than lower doses; however, there were only 3 incidents of “feeling abnormal” and 9 incidents of flushing (unrelated to incidents of hypotension) with Ryanodex treatment making an assessment of their dose dependency impossible. These TEAEs did not occur more frequently with high doses of Dantrium. The other TEAEs that occurred at the higher dose, but did not exhibit dose dependency included nausea, vomiting, dysphagia, fatigue, somnolence and dysphonia.

In summary, based on the limited data available from the clinical trials, there were no TEAEs which appeared to be dose dependent following treatment with either Ryanodex or Dantrium.

Table 12. Summary of Treatment Emergent Adverse Events by System Organ Class

System Organ Class	Dantrium					Ryanodex							
	1.0 mg/kg	1.75 mg/kg	2.0 mg/kg	2.25 mg/kg	2.5 mg /kg	1.0 mg/kg Injected over 30 s	1.75 mg/kg Infused over 5 m	1.75 mg/kg Injected over 30 s	1.75 mg/kg Injected over 1 m	2.0 mg/kg Injected over 30 s	2.0 mg/kg Injected over 1 m	2.25 mg/kg Injected over 1 m	2.5 mg/kg Injected over 1 m
N	3	4	4	4	16	7	4	9	4	2	4	4	15
Cardiac disorders						1	1	2		2			2
Eye disorders	1				1		2	2	1				
Gastro-intestinal disorders		3	1	1	3	1	3	7		1	1		5
General disorders and administration site conditions			1		3	3	3	9		2	1		4
Musculo-skeletal and connective tissue disorders			1		1	2	2	4					1
Nervous system disorders	2		2	2	4	3	4	9	1	2	1	1	3
Psychiatric disorders						1	3	3		1			
Respiratory, thoracic and mediastinal disorders					1		2	4		2			4
Vascular disorders					1		1			1		1	7

7.5.2 Time Dependency for Adverse Events

The Applicant did not make an assessment of the time dependency for the adverse events.

In an effort to assess the time dependency of the adverse events, all AEs that began within one hour of the initiation of study drug administration were excluded from the 226 treatment-emergent adverse events (TEAEs). There were a total of 50 TEAEs that remained. About half (24) of these TEAEs began more than 24 hours following study drug administration initiation; only seven of which were considered by the Investigators as unrelated or probably not related to study drug. The onsets of TEAEs relative to the initiation of study drug administration are summarized in the Table 13 below.

Table 13. Summary of onset times for TEAEs by treatment group

Onset time (hours after initiation of study drug administration)	Number of TEAEs			
	Dantrium (n = 31)	Placebo (n = 4)	Ryanodex (n = 49)	Total (n = 84)
1	0	4	2	6
2	2	0	6	8
3	0	0	2	2
4	2	2	0	4
5	0	0	2	2
6	0	0	1	1
8	0	0	1	1
9	1	0	0	1
11	1	0	0	1
>24	7	0	17	24
Total	13	6	31	50

The TEAEs occurring more than an hour following initiation of study drug administration are summarized in Table 14 below. As indicated in the table, the TEAEs occurring most frequently were gastrointestinal in nature for both Ryanodex and Dantrium treatments. Of the 31 TEAEs occurring with Ryanodex treatment, all were mild or moderate in severity, and most (14) occurred with the 2.5 mg/kg dose administered over 1 minute followed by 13 TEAEs that occurred with the 30 second administration of 1, 1.75, and 2 mg/kg doses.

In summary, most of the Ryanodex related TEAEs occurred within one hour of initiation of study drug administration; those occurring after one hour were mild to moderate in severity, occurred more frequently with rapid infusion and the highest dose of Ryanodex, and were readily monitored and easily treated if necessary. All resolved within 72 hours.

Table 14. TEAEs occurring more than 1 hr after initiation of study drug administration

System Organ Class	Preferred Term	Treatment		
		Dantrium	Placebo	Ryanodex
Blood and lymphatic system disorders	Neutropenia	1	0	0
Cardiac disorders	Atrioventricular block	0	0	1
	Palpitations	0	0	1
	Tachycardia	0	0	1
Eye disorders	Asthenopia	1	0	0
Gastrointestinal disorders	Abdominal pain	0	0	1
	Nausea	2	1	7
	Vomiting	2	0	1
General disorders and administration site conditions	Fatigue	0	0	2
	Feeling abnormal	0	0	2
	Feeling hot	0	0	1
	Infusion site pain	0	0	1
	Vessel puncture site haematoma	0	1	0
	Vessel puncture site haemorrhage	0	1	0
	Vessel puncture site swelling	0	2	0
Infections and infestations	Otitis externa	1	0	0
Musculoskeletal and connective tissue disorders	Back pain	1	0	0
	Musculoskeletal chest pain	0	0	1
	Pain in extremity	1	0	1
	Sensation of heaviness	0	0	1
Nervous system disorders	Dizziness	0	1	1
	Headache	3	0	1
	Hypotonia	1	0	0
Psychiatric disorders	Inappropriate affect	0	0	1
Renal and urinary disorders	Chromaturia	0	0	1
Respiratory, thoracic and mediastinal disorders	Dysphonia	0	0	1
Skin and subcutaneous tissue disorders	Hyperhidrosis	0	0	1
Vascular disorders	Flushing	0	0	4

7.5.3 Drug-Demographic Interactions

The Applicant analyzed treatment emergent adverse events (TEAEs) by gender across all treatment groups. There were 35 males and 14 females in the Ryanodex treatment groups and 25 males and 6 females in the Dantrium treatment groups. The Applicant noted that although the overall incidence of AEs was similar between males and females, the number of female subjects reporting at least one AE was lower in all Ryanodex and Dantrium treatment groups. In addition, they reported the following gender-based findings:

1. Female subjects reported fewer eye disorders and gastrointestinal disorders in comparison to male subjects.
2. Male subjects reported higher numbers of AEs of diplopia and blurred vision, as well as dysphagia and nausea in comparison to female subjects.
3. Male subjects also reported a higher number of nervous system AEs, including dizziness, dysarthria, and somnolence.

The Applicant performed a separate analysis of subjects treated with the highest dose studied, the 2.5 mg/kg dose. While the number of male and female subjects reporting at least one AE was similar between treatment groups, males were more likely to report multiple events and only male subjects reported dysphonia and flushing. Males also reported a higher number of gastrointestinal disorders (dysphagia and nausea). Only female subjects reported musculoskeletal and connective tissue disorders (back pain and pain in an extremity).

The reasons for the gender differences are unknown. Based on the small numbers of subjects, the number of doses and administration rates studies, and the relatively small numbers of TEAEs separating the genders for the different treatment groups, the Applicant concluded that, overall, there were no clinically meaningful differences in safety assessments by gender.

The Applicant's assertion that the differences in TEAEs based on gender are not clinically relevant is supported by the limited available. However, the numbers of subjects studied, particularly female subjects, as well as the variety of doses of Ryanodex and administrations times that were evaluated for safety suggest that there are inadequate data to determine whether a gender-based difference in safety exists for any method of dosing. While there is no physiological basis for a gender-based difference to exist, if the differences in TEAEs that were observed are gender based, they do not substantially affect the overall safety of the product for either gender as the TEAEs were not life threatening, were mostly mild or moderate in severity, easily monitored, and resolved with minimal to no intervention.

The Applicant analyzed treatment-emergent adverse events by race and found that the overall incidence of subjects with at least 1 treatment-emergent adverse event was comparable between white and non-white subjects in both the Ryanodex and Dantrium

treatment groups. There were an increased number of white subjects in both the Ryanodex and Dantrium treatment groups who exhibited a higher incidence of gastrointestinal disorders (dysphagia, nausea), general disorders, respiratory disorders (especially dysphonia), vascular disorders (flushing), and somnolence, in comparison to non-white subjects. They concluded that, overall, there were no clinically meaningful differences in the incidence and pattern of adverse events between the races assessed, but noted that the number of non-white subjects dosed was relatively small.

Given the small number of non-white subjects enrolled in the trials and the number of treatment groups evaluated, there were too few subjects to adequately determine whether race or ethnicity influences the safety of Ryanodex.

The Applicant compared treatment-emergent adverse events for the two active treatment groups based on body mass index (BMI) groupings of $< 25 \text{ kg/m}^2$ and $\geq 25 \text{ kg/m}^2$. The Ryanodex group included 21 subjects who had a BMI $< 25 \text{ kg/m}^2$ and 28 subjects with a BMI of $\geq 25 \text{ kg/m}^2$, while the Dantrium group had 24 subjects with a BMI $< 25 \text{ kg/m}^2$ and 7 subjects with a BMI of $\geq 25 \text{ kg/m}^2$. They reported that the overall incidence of TEAEs was similar between BMI subgroups; however, in general, the Ryanodex $\geq 25 \text{ kg/m}^2$ BMI subgroup had a higher incidence of TEAEs in most of the body systems. Specifically, the TEAEs including asthenia, dizziness, dysarthria and somnolence occurred more frequently in the Ryanodex $\geq 25 \text{ kg/m}^2$ BMI subgroup than in the Ryanodex $< 25 \text{ kg/m}^2$ subgroup and both the Dantrium BMI subgroups. The low number of subjects in the Dantrium subgroup of $\geq 25 \text{ kg/m}^2$ BMI ($n = 7$) in comparison to the Ryanodex subgroup of $\geq 25 \text{ kg/m}^2$ BMI ($n = 28$) may mask a difference that also occurs with higher BMI individuals treated with Dantrium. As with other analyses of adverse events, the Applicant noted that the observation of differences in the incidence of adverse event between the treatment groups is complicated by the fact that Dantrium was not administered at the (b) (4) site.

As with the other analyses, the number of subjects and variety of treatment groups prohibits the determination of what impact, if any, BMI has on the safety profile of Ryanodex. While there is no physiological basis for suspecting a difference to exist, it is possible that individuals with greater BMIs may be more sensitive to some of the TEAEs observed, i.e., weakness, asthenia, and dyspnea, due to the impact it may have on their mobility and their ability to expand their chest walls and move their diaphragms by virtue of their increase weight for their height.

The Applicant analyzed the treatment-emergent AEs for the two active treatment groups by age group, i.e., subjects aged 18-35 years old and subjects older than 35 years. They found that there was a somewhat higher incidence of AEs in the 18 to 35 year old age group, with this age group reporting an increased number of gastrointestinal disorders (dysphagia), eye disorders (blurred vision, diplopia), general disorders (asthenia, fatigue), and nervous system disorders (somnolence). They did not conclude whether the differences observed were clinically relevant; however, as with the other

demographics, the numbers of subjects in each treatment group was too small to be able to discern clinically relevant differences based on very small differences in age. For Ryanodex treatments, there were 39 subjects 18-35 years of age; there were 25 subjects in the same age range treated with Dantrium. There were only 10 subjects >35 years old who were treated with Ryanodex, and 6 subjects that age range who were treated with Dantrium. There is no physiological basis to the increased incidence of TEAEs in younger subjects, and no reason to expect an increase in TEAEs for older ones. The numbers of subjects are too small to distinguish any differences; the most that can be concluded from the data is that no signal was observed for any of the age-based treatment groups.

In summary, the numbers of subjects enrolled in the two treatment groups, i.e., Ryanodex and Dantrium, were too small to allow clinically meaningful differences based on demographic parameters to be discerned. There was no physiological basis to expect a demographic difference to exist. The TEAE data did not indicate a safety signal for the use of Ryanodex in any single demographic group, and they did not indicate a clear difference between Ryanodex and Dantrium for any particular demographic subgroup.

7.5.4 Drug-Disease Interactions

The Dantrium label does not include any information on known or potential drug-disease interactions. The Applicant has not evaluated the use of Ryanodex in a population other than healthy young adults, and therefore, has no information to include in the label in this regard.

It is likely that Ryanodex will be administered to patients with comorbidities and underlying disease conditions. While malignant hyperthermia (MH) is not usually associated with other medical conditions, its effects, and those of the treatments rendered, have the potential to substantially impact patients' homeostasis and the management of their medical conditions. Given the acute use of Ryanodex in a life-threatening situation, it would be difficult to discern drug-disease interactions in the clinical setting, and the number of diseases that would have to be evaluated, based on those typically occurring in patients presenting for surgery, are too numerous for evaluation in controlled clinical trials. While the lack of information is disconcerting, the intensive care that is provided for patients in the operating room, where most cases of MH initiate and are treated, and in the hospital setting where patients are generally followed for 48-72 hours after the MH crisis has been broken, should allow appropriate monitoring of their underlying medical conditions and timely interventions to treat them as needed.

7.5.5 Drug-Drug Interactions

The Applicant did not conduct any studies to evaluate the possibility of drug-drug interactions involving Ryanodex. For these interactions, they are relying on information contained in the Dantrium label, which provides the following information regarding drug-drug interactions that occur with dantrolene:

Dantrium is metabolized by the liver, and it is theoretically possible that its metabolism may be enhanced by drugs known to induce hepatic microsomal enzymes. However, neither phenobarbital nor diazepam appears to affect Dantrium metabolism. Binding to plasma protein is not significantly altered by diazepam, diphenylhydantoin, or phenylbutazone. Binding to plasma proteins is reduced by warfarin and clofibrate and increased by tolbutamide.

Cardiovascular collapse in patients treated simultaneously with verapamil and dantrolene sodium is rare. The combination of therapeutic doses of intravenous dantrolene sodium and verapamil in halothane/alpha-chloralose anesthetized swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalemia. It is recommended that the combination of intravenous dantrolene sodium and calcium channel blockers, such as verapamil, not be used together during the management of malignant hyperthermia crisis until the relevance of these findings to humans is established.

Administration of dantrolene may potentiate vecuronium-induced neuromuscular block.

The Applicant proposes the following wording in Section 7, Drug Interactions, of the Ryanodex package insert:

7.1 Calcium Channel Blockers

Cardiovascular collapse in association with marked hyperkalemia has been reported in patients receiving dantrolene in combination with calcium channel blockers. (b) (4)

[Redacted text block]

[Redacted text block] (b) (4)

(b) (4)



Given the overall similarity in the formulations of Ryanodex and Dantrium and in their indications, incorporation of the information from the Dantrium label above into the Ryanodex label is appropriate.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant has relied upon the information in the Dantrium label to address the potential for dantrolene to be carcinogenic. The Dantrium label states the following in this regard:

Sprague-Dawley female rats fed Dantrium for 18 months at dosage levels of 15, 30, and 60 mg/kg/day showed an increased incidence of benign and malignant mammary tumors compared with concurrent controls. At the highest dose level (approximately the same as the maximum recommended daily dose on a mg/m² basis), there was an increase in the incidence of benign hepatic lymphatic neoplasms.

In a 30-month study in Sprague-Dawley rats fed dantrolene sodium, the highest dose level (approximately the same as the maximum recommended daily dose on a mg/m² basis) produced a decrease in the time of onset of mammary neoplasms. Female rats at the highest dose level showed an increased incidence of hepatic lymphangiomas and hepatic angiosarcomas.

The only drug-related effect seen in a 30-month study in Fischer-344 rats was a dose-related reduction in the time of onset of mammary and testicular tumors.

A 24-month study in HaM/ICR mice revealed no evidence of carcinogenic activity.

The significance of carcinogenicity data relative to use of Dantrium in humans is unknown.

Dantrolene sodium has produced positive results in the Ames S. Typhimurium bacterial mutagenesis assay in the presence and absence of a liver activating system.

The Applicant proposes to use the following wording in their package insert:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Sprague-Dawley female rats fed dantrolene sodium for 18 months at dosage levels of 15, 30, and 60 mg/kg/day showed an increased

incidence of benign and malignant mammary tumors compared with concurrent controls. At the highest dose level (approximately the same as the maximum recommended daily dose on a mg/m² basis), there was an increase in the incidence of benign hepatic lymphatic neoplasms. In a 30-month study in Sprague- Dawley rats fed dantrolene sodium, the highest dose level (approximately the same as the maximum recommended daily dose on a mg/m² basis) produced a decrease in the time of onset of mammary neoplasms. Female rats at the highest dose level showed an increased incidence of hepatic lymphangiomas and hepatic angiosarcomas.

The only drug-related effect seen in a 30-month study in Fischer-344 rats was a dose-related reduction in the time of onset of mammary and testicular tumors. A 24-month study in HaM/ICR mice revealed no evidence of carcinogenic activity.

The significance of carcinogenicity data relative to use of Ryanodex in humans is unknown.

Mutagenesis

Dantrolene sodium has produced positive results in the Ames S. Typhimurium bacterial mutagenesis assay in the presence and absence of a liver activating system.

The proposed wording accurately conveys the information contained in the Dantrium label.

7.6.2 Human Reproduction and Pregnancy Data

The Applicant provided no data on the effects of Ryanodex or dantrolene sodium on human reproduction and pregnancy. They have utilized the Dantrium label for this information and have incorporated similar wording into their proposed label. The Dantrium label states the following in this regard and classifies the product as Pregnancy Category C:

Dantrolene sodium administered to male and female rats at dose levels up to 45 mg/kg/day (approximately 1.4 times the maximum recommended daily dose on a mg/m² basis) showed no adverse effects on fertility or general reproductive performance.

Dantrium has been shown to be embryocidal in the rabbit and has been shown to decrease pup survival in the rat when given at doses seven

times the human oral dose. There are no adequate and well-controlled studies in pregnant women.

Dantrium Intravenous should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The Applicant proposes to use the following wording in their package insert:

Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Impairment of Fertility

Dantrolene sodium administered to male and female rats at dose levels up to 45 mg/kg/day (approximately 1.4 times the maximum recommended daily dose on a mg/m² basis) showed no adverse effects on fertility or general reproductive performance.

8.1 Pregnancy

Pregnancy Category C.

 (b) (4)
Ryanodex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The approach of the Applicant for providing this information is acceptable as is the way they have incorporated it into their proposed label.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant has provided no information on the use of Ryanodex or dantrolene sodium in the pediatric population and no assessments of their effects on growth. There is no information in the Dantrium label regarding the product's safety in pediatric patients or its effects on growth and development.

Based on the mechanism of action of dantrolene, its acute use in a life-threatening situation, and its safety profile in the adult population, there is no indication that Ryanodex would be expected to pose any special risks to pediatric patients or have any untoward effects on growth and development in this patient population. The Applicant has included the following statement in their proposed label, which is accurate and appropriate based on the information available to date.

(b) (4)



7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant has relied upon the Dantrium label for information regarding dantrolene overdose. The Dantrium labeling includes the follow statements in the section titled Overdosage:

Because **Dantrium Intravenous** must be administered at a low concentration in a large volume of fluid, acute toxicity of **Dantrium** could not be assessed in animals. In 14-day (subacute) studies, the intravenous formulation of **Dantrium** was relatively non-toxic to rats at doses of 10 mg/kg/day and 20 mg/kg/day. While 10 mg/kg/day in dogs for 14 days evoked little toxicity, 20 mg/kg/day for 14 days caused hepatic changes of questionable biologic significance.

Symptoms which may occur in case of overdose include, but are not limited to, muscular weakness and alterations in the state of consciousness (e.g., lethargy, coma), vomiting, diarrhea, and crystalluria.

For acute overdosage, general supportive measures should be employed.

Intravenous fluids should be administered in fairly large quantities to avert the possibility of crystalluria. An adequate airway should be maintained and artificial resuscitation equipment should be at hand.

Electrocardiographic monitoring should be instituted, and the patient carefully observed. The value of dialysis in **Dantrium** overdose is not known.

The Applicant has rearranged these statements and has incorporated some of their own animal findings to develop the following proposed labeling for Section 10 Overdosage:

(b) (4)



(b) (4)



(b) (4)



10.3 Management of Overdosage

(b) (4)



The proposed labeling is appropriate in its content and layout and in its incorporation of information specific to Ryanodex.

There is no known potential for or reports of the abuse of dantrolene sodium. Similarly, there is no known potential for or reports of rebound effects when the product is discontinued, which would be expected given its acute use for malignant hyperthermia.

7.7 Additional Submissions / Safety Issues

An inspection by Xikui Chen from the Office of Scientific Investigations (OSI) of the serum samples used for pharmacokinetic analyses revealed that multiple samples were orange or red in color suggesting hemolysis had occurred (see Figure 1).

Figure 1. Photograph of PK plasma specimens taken by OSI



This finding raised three concerns:

1. Did hemolysis occur, and if so, did it affect the analytical techniques used to determine dantrolene concentrations?
2. Is dantrolene sequestered in red blood cells to an extent that hemolysis would substantially increase the drug concentrations reported in the PK studies?
3. Does dantrolene cause hemolysis?

The first concern was already addressed by the Applicant in the original NDA submission. The effect of hemolysis on the bioanalytical techniques used to assess measure dantrolene levels was relatively low and considered acceptable by Drs. Nallani and Xu of the Clinical Pharmacology team.

To address the issue of sequestration of dantrolene in red blood cells, the Applicant assessed the relative recovery of dantrolene after spiking human whole blood with Ryanodex (or dantrolene sodium, USP) at 3 dantrolene concentrations, based on the using the concentrations present in quality control (QC) High, Mid and Low samples. The volume of Ryanodex, or dantrolene sodium, USP, added to target a final dantrolene

plasma concentration equal to either the QC High, Mid, or Low samples assumed that 100% of dantrolene would partition into plasma, i.e., the amount of Ryanodex added to reach the target dantrolene plasma concentration specified for each QC sample assumed there would be with no sequestration in blood cells. The distribution of the added quantity of dantrolene assumed 50% of total blood sample volume was cellular in nature, resulting in final dantrolene whole blood concentrations of 10,000, 750 and 75 ng/mL. After addition of Ryanodex (or dantrolene sodium, USP) to human whole blood samples at each QC concentration level, the blood samples were gently mixed and placed into water bath at 37° C for 1 hour. At 1 hour, all samples were removed from the water bath, and two sets of blood samples per QC concentration level were spun in a centrifuge at 10° C at 3600 rpm for 10 minutes to allow recovery of plasma. Two additional sets of blood samples per QC concentration level were treated to induce complete hemolysis prior to being spun in a centrifuged under the same conditions to allow recovery of plasma. After centrifugation, samples were photographed to visually document the condition of the plasma. All resultant plasma from the samples was analyzed for dantrolene concentration according to previously used bioanalytical methods. The results of the study are summarized in Table 15 below, and a photograph of the plasma for the Low, Mid, and High QC samples are seen in Figure 2.

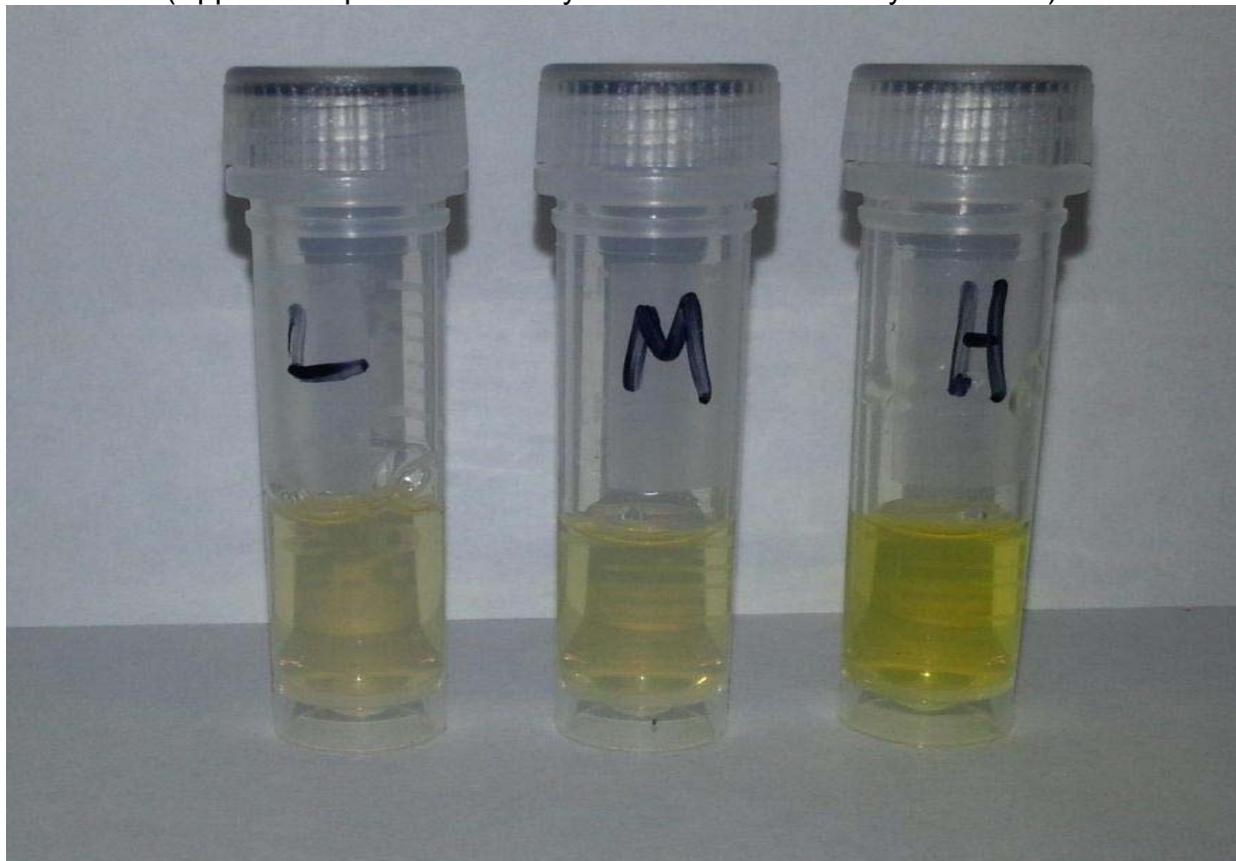
Table 15. Hemoglobin concentrations in nonhemolyzed and hemolyzed plasma samples (based on Table 2 p. 3 Summary of Draft Data for Study 1773-025)

Test Article added to Whole Blood	QC Level	Nominal Plasma Concentration ^A (ng/mL)	Sample Component Analyzed ^B	Mean Plasma Dantrolene Concentration (ng/mL)	% Difference in Concentration (relative to Plasma Sample)	% Recovery from Nominal Plasma Concentration
Dantrolene Sodium, USP	QC Low	150	Plasma	47.6	NA	31.7
			Supernatant	58.2	22.2	38.8
	QC Mid	1,500	Plasma	555	NA	37.0
			Supernatant	604	8.8	40.3
	QC High	20,000	Plasma	10,257	NA	51.3
			Supernatant	8,415	-18.0	42.1
Ryanodex	QC Low	150	Plasma	45.1	NA	30.1
			Supernatant	57.8	28.1	38.5
	QC Mid	1,500	Plasma	510	NA	34.0
			Supernatant	588	15.3	39.2
	QC High	20,000	Plasma	9,253	NA	46.3
			Supernatant	7,785	-15.9	38.9

^A Assumes all dantrolene is in the plasma compartment of whole blood (100% partition) after addition of the test article.

^B Plasma = specimen is from intact blood; Supernatant – specimen is from hemolyzed blood
 NA = not applicable

Figure 2. Photograph of plasma samples with low, mid and high concentrations of dantrolene (Appendix 2 p. 5 of Summary of Draft Data for Study 1773-025)



Based on this information, the Applicant concluded the following:

1. The color of plasma isolated from blood spiked with Ryanodex or dantrolene sodium, USP (at all QC concentration levels) did not demonstrate a notable difference in color between samples.
2. Measured dantrolene concentration for plasma or supernatant (from hemolyzed samples) from human whole blood treated with Ryanodex and dantrolene sodium, USP, were comparable.
3. In the QC low (nominal plasma concentration 150 ng/mL) and mid (nominal plasma concentration 1,500 ng/mL) concentration samples, 9% to 28% more dantrolene was evident in the supernatant from the hemolyzed blood samples than was present in the corresponding plasma obtained from non-hemolyzed blood. In contrast, at the QC high (nominal plasma concentration 20,000 ng/mL) concentration level, 16% to 18% less dantrolene was liberated from whole blood after complete hemolysis versus the levels observed in plasma.

Lastly, the Applicant evaluated the effects of different doses of dantrolene on the color of plasma and looked for a correlation between the presence of hemoglobin in the samples and any color changes. To do this, they evaluated the 1,156 plasma samples from Part 2 of Trial EGL-Dantrolene-1201 using both a visual sample color grading system and an evaluation of hemolytic index (HI). A color scale (defining “yellow”, “orange”, and “red”) was prepared using study samples representative of each color category (2 samples for “yellow”, 2 for “orange”, and 1 for “red”) to ensure uniformity in color grading for the visual assessment. The HI was evaluated using an analyzer with a reagent for determination of hemoglobin in plasma. This method of analysis was chosen because the usual enzymatic-assay based quantification of hemoglobin concentration was not possible due to the K₂EDTA matrix used for the bioanalytical sample processing (EDTA is known to interfere with the enzymatic assay). In the event that the hemolytic index could not be determined by the instrumentation, hemolytic status was assessed by visual inspection. Table 16 below shows how the HI corresponded to hemoglobin concentrations in the plasma samples.

Table 16. Hemolytic Index (Table on p. 1 of Draft Study Report for Study 1773-022)

Hemolytic Index (HI)	Hemoglobin Concentration (mg/dL)	Hemolysis Status
0	<50	No hemolysis
1	50-99	Slight hemolysis
2	100-199	Hemolyzed
3	200-299	Moderately hemolyzed
4	300-500	Grossly hemolyzed
6 ^A	NA	NA

^A If the analyzer returned a sample HI result of 6, the sample was reanalyzed. Following a repeat HI result of 6, the sample was inspected for visual evidence of hemolysis (in accordance using the specimen chart. If no visible hemolysis was present, the HI value was suppressed and a comment of “no visible hemolysis” was reported.

The following findings were reported for this analysis:

1. A total of 1,112 (of the 1,156) samples were noted as “yellow” (i.e., normal plasma color), 43 samples were noted as “orange”, and one sample was noted as “red.”
2. Hemolytic index was determined for 1,125 of the 1,156 samples
 - a. 1,068 samples returned a HI value of 0
 - b. 51 samples returned a HI value of 1
 - c. 5 samples a HI value of 2
 - d. 1 sample returned a HI of 3.
3. For the remaining 31 samples a HI value of 6 was returned in a repeat analysis and, these samples were visually inspected and were determined to have no visual evidence of hemolysis. The independent sample color grading result

recorded for these 31 samples showed 28 samples to be “yellow” in color and 3 samples to be “orange”.

Based on these findings the following conclusions were drawn by the Applicant:

1. There appears to be no correlation between the measured dantrolene plasma concentration and either sample color, hemolysis status, or approximate hemoglobin concentration of samples.
2. For the 1,125 samples with an HI value of between 0 and 3 there was a very good correlation between visual grading and hemolysis status (as determined by HI); yellow samples predominantly indicating an HI score of 0 (18 of the 1,112 yellow samples returned an HI of 1), orange samples indicating an HI score of 1 or 2 (2 orange samples had an HI of 0), and the red sample displaying an HI score of 3.
3. Five of the 61 (8%) predose samples were visually described as orange, whereas only 4% of all the samples were graded as orange or red.
4. There are no data to indicate an impact on dantrolene plasma concentration resultant from hemolysis.

This information was reviewed by the Clinical Pharmacology team, and they concurred with the Applicant that the bioanalytical techniques used to measure plasma dantrolene concentrations were not substantially affected by hemolysis and that the levels of hemolysis observed in the PK samples collected in Trial 1201 did not substantially affect the plasma dantrolene concentrations or alter the PK characteristics evaluated in the study. Lastly, the HI and color grading results of each of the plasma samples were reviewed to determine whether there was an association between dantrolene concentration and occurrence or extent of hemolysis. No such association was observed; it appeared that some other factor in the obtaining or subsequent handling of the blood samples was responsible for the limited amount of hemolysis that was observed in less than 5% of the post-study drug PK plasma samples.

Based on the information above, there is no evidence that:

1. Hemolysis affects the bioanalytical methods used to measure plasma concentrations of dantrolene.
2. Dantrolene causes hemolysis.
3. the occurrence of hemolysis in a limited number of PK plasma samples did not significantly altered the PK characteristics evaluated in the clinical study.

The Applicant submitted a 120-day safety update on May, 13, 2014, in which they noted there were no new clinical or animal studies conducted, or completed post-submission of the application, and that a literature search spanning over the publishing date period from December 7, 2013, to May 2, 2014, revealed no new information that may reasonably affect the contraindications, warnings, precautions, or adverse reactions sections in the proposed labeling.

8 Postmarket Experience

Ryanodex has not been approved or marketed outside of the United States; therefore, there is no postmarketing experience with this product. There is, however, a substantial postmarketing experience with the Dantrium IV product, which shares the same indications being sought for Ryanodex; although the formulations differ both in terms of the concentrations of dantrolene sodium and the amount of mannitol administered to patients, i.e., Dantrium contains 0.3 mg/mL of dantrolene and 50 mg/mL of mannitol, whereas Ryanodex contains 50 mg/mL of dantrolene and 25 mg/mL of mannitol. To determine whether the postmarketing experience indicates safety concerns for the use of Dantrium that are not included in the current label, the Division of Pharmacovigilance II, in the Office of Pharmacovigilance and Epidemiology, were consulted to review the information contained FAERS database. They found that from January 1, 1969 to April 11, 2014, there were 354 reports for injectable dantrolene reported in FDA's Adverse Event Reporting System (FAERS). Of those reports, 113 involved prophylaxis of or treatment for anesthesia-induced malignant hyperthermia. Most of the reports were considered labeled events or were confounded by the underlying surgical indication, comorbidities, or concomitant medications. They did identify identified 20 cases of seizure and two cases of respiratory depression (in patients treated for neuroleptic malignant syndrome, not malignant hyperthermia) that were temporally associated with injectable dantrolene, and for which they could not exclude an association to dantrolene. (b) (4)

They also performed a search of the published medical literature and identified reports of three unlabeled events; none of which indicated a new safety signal.

They concluded that there were not any new safety signals for dantrolene injection. Their recommendations for labeling changes regarding seizures and respiratory depression are as follows:

- In the Warning about monitoring vital signs when using dantrolene for (b) (4) of malignant hyperthermia, revise to “Since ~~the effect of disease state and other drugs on~~ Dantrium related skeletal muscle weakness, including possible respiratory depression, cannot be predicted, patients who receive i.v. IV Dantrium ~~preoperatively~~ should have vital signs monitored.”
- Seizures: In the Adverse Events section, remove seizures from the statement, “None of the serious reactions occasionally reported with long-term oral Dantrium use, such as hepatitis, ~~seizures~~, and pleural effusion with pericarditis, have been reasonably associated with short-term Dantrium Intravenous therapy.”

From a clinical perspective, the recommended changes to the label should be made.

9 Appendices

9.1 Literature Review/References

The literature was reviewed only to identify new safety concerns for dantrolene sodium. This review was conducted by the Division of Pharmacovigilance II, in the Office of Pharmacovigilance and Epidemiology, and their findings are described in Section 8 above.

Published literature was not relied upon to support either the clinical efficacy or safety of Ryanodex.

9.2 Labeling Recommendations

Recommendations for changes to the proposed labeling for Ryanodex are made to the copy of the label below. Changes are in red font with recommended insertions underlined and recommended deletions crossed out. These recommendations are to serve as a starting point for internal discussions and, later, labeling negotiations with the Applicant.

Full Prescribing Information

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill. The redaction covers the entire content of the 'Full Prescribing Information' section. A small label '(b) (4)' is positioned at the top left corner of the redacted area.

13 Page(s) of draft labeling has been Withheld in Full
as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

An Advisory Committee was not convened to review data or provide input regarding any issue related to this application; there were no issues identified that warranted such input.

9.4 Review of Clinical Trials

Detailed descriptions of the two clinical trials conducted in support of this application are provided below. Trial 1201A is the trial that was terminated following major amendments to the protocol, which required the trial to be conducted with a new clinical research organization. Trial 1201 is the trial that was conducted to completion and provides the majority of the safety and pharmacokinetic data for this application. Where possible in the safety analyses in Section 7 above, the data from the two trials were combined. Following the descriptions of the trials, there are comments about their execution, summaries of the key findings, and discussion of the implications of the trial findings for the evaluation of the safety of Ryanodex.

9.4.1 EGL-Dantrolene-1201A

Title: Pharmacokinetics and Safety of Dantrolene Sodium Suspension (Ryanodex®) compared to Dantrolene Sodium for Injection (Dantrium® Intravenous) in Healthy Volunteers

Dates: August 2, 2012 through October 8, 2012

Objectives

Primary Objective:

To characterize the single dose PK profile of Ryanodex in conscious healthy volunteers

Secondary Objectives:

- To determine the MTD of Ryanodex in conscious healthy volunteers
- To compare the single-dose PK profile and evaluate the safety and tolerability of Ryanodex and Dantrium in conscious healthy volunteers

Endpoints

Efficacy: There were no assessments made of efficacy

Pharmacokinetics:

- C_{max}
- T_{max}
- $t_{1/2}$
- AUC_{0-last}
- AUC_{0-24}
- AUC_{0-inf}
- Cl_{obs}
- V_z
- V_{dss} (dantrolene only)
- λ_z
- AUMC

Safety

- Adverse Events
- Physical examinations
- Vital Signs
- Electrocardiogram
- Oxygen Saturation

- Spirometry
- etCO₂ - etCO₂ monitoring was added by protocol Amendment to better assess respiratory insufficiency, at the investigator's discretion.
- MIP and MEP - MIP and MEP determination was performed using a respiratory pressure meter. On each time point that MIP and MEP were measured, 3 serial, replicate measurements were made approximately 1 minute apart.
- Clinical Laboratory Assessments – Includes biochemistry profile, complete blood count with differential, urinalysis and coagulation profile.
- Head Lift - The subject, while reclining, was asked to lift his/her head from the pillow/chair for at least 5 seconds at the times specified to characterize muscle weakness. Effort was assessed categorically as either successful or unsuccessful. Once the subject began to ambulate, this activity was discontinued.
- Grip Strength - Hand grip strength determination was performed at the times specified to characterize muscle weakness. Measurements were recorded, as instructed in the Training Manual provided by the Sponsor. On each occasion that hand grip strength was measured post dose, the measurement was made three times for each hand. A rest period of approximately 30 seconds took place between each individual measurement.
- Stair Climb - Subjects were asked to walk up one flight of stairs of approximately 2.5-3 m in total height at the times specified to determine recovery from muscle weakness. Ability to do so was a prerequisite to discharge.
- Subjective Status (Likert Scales) - Likert scales were administered at the times specified and used to assess subjective status. Subjects were asked about the following attributes pre- and post-dose:
 - Weakness. – If weakness is noted, where? Generalized, arms, legs, other (specify)
 - Dyspnea (described to subject as “difficulty breathing or shortness of breath”)
 - Dizziness (described to subject as “dizzy, light-headed, feeling faint, giddiness, woozy”)
 - Nausea
 - Fatigue

Subjects responded by rating each condition on a 0 through 4 numeric scale, 0 meaning “none at all” and 4 as “severe/bad as can be.”

Inclusion Criteria (verbatim, pp. 33-34 of final study report)

1. Subjects could be male or female.
2. Women of childbearing potential must have agreed to use an effective non-systemic form of contraception, such as a diaphragm and spermicide,

intrauterine device (IUD), or condom and spermicide used by partner, during the study and for at least one month after its completion.

- a) For females to be considered of non-childbearing potential due to menopause, the onset of menopause must have been at least one year prior to study entry. Females that were surgically sterile were eligible.
3. Men must have used an effective form of contraception, such as a condom and spermicide or a diaphragm or IUD used by partner, during and for at least one month after completion of study.
4. Females must have been nonpregnant and nonlactating.
5. Subjects were aged 18 to 45 years at study entry.
6. Subjects had a BMI between 18-32 kg/m², inclusive.
7. Subjects had a minimum body weight 50 kg (110 lbs); maximum 100 kg (220 lbs).
8. Subjects were healthy as determined by the investigator based on history, physical examination, clinical laboratory tests and 12-lead ECG.
9. Subjects must have had adequate venous patency to allow infusion of the planned dose of Ryanodex in less than 30 seconds and, for participants in the crossover part of the study, of Dantrium over 15 - 30 minutes, as determined by the Investigator at examination:
 - a) The IV line must have had adequate capacity to allow, for a 100 kg subject receiving 5 mg/kg Ryanodex, infusion of at least 20 mL saline/minute by infusion pump without danger of infiltration. Lighter subjects and those receiving lower doses received proportionally less Ryanodex.
 - b) Additionally, in Part 2 of the study, the IV line must have had adequate capacity to allow infusion of the required dose of Dantrium at an infusion rate of approximately 60 mL/min. For the planned dose, 2.5 mg/kg and with the heaviest subject allowed per protocol, 100 kg, the maximum saline infusion rate was 25 mL/min with a total volume of 750 mL over 12.5 minutes at an infusion rate of 60 mL/min. At lower doses and for smaller subjects, the infusion duration was less at the same infusion rate.
 - c) In addition, for both parts of the study, veins in the contralateral arm must have been large enough to accommodate an indwelling catheter, if necessary, for blood sampling for the first 48 hours post-dose and tolerant to repeated venipuncture for blood sampling throughout the study.
10. Subjects must have agreed to abstain from alcohol consumption for 2 weeks prior to receiving study medication and for the duration of the study.
11. Subjects must have been willing and able to remain in the study unit for the entire duration of each confinement period and return for the scheduled follow-up visits.
12. Subjects must have provided voluntary written informed consent for participation.
13. Subject must have had normal lung function, defined as force vital capacity (FVC) \geq 80%, force expiratory volume (FEV1) \geq 80%, and forced expiratory flow (FEF) 25-75 \geq 65% of predicted normal.
14. Subjects must have had MIP and MEP \geq 80% of normal predicted pressure

15. Subjects must have demonstrated, in the opinion of the Investigator, a high probability of safely completing the study.

Exclusion Criteria (verbatim, p. 35-36 of final study report)

1. Subjects with any current or history of any clinically significant medical condition, such as cardiovascular, pulmonary, endocrine, muscular, gastrointestinal, hepatic or psychiatric disorders, which might have, in the opinion of the investigator, jeopardized the safety of the subject or affected the validity of study results.
2. Subjects who had used any prescription medication (including dantrolene sodium) within 30 days prior to test drug administration or who were taking any medication either prescription or over-the-counter (OTC), chronically, intermittently or short-term for any condition, with the following limited exceptions:
 - a) Subjects taking prophylactic aspirin may have participated as long as they had never had any cardiovascular signs or symptoms, had no evidence of cardiovascular disease and could safely stop the medication(s) for at least two weeks before receiving study medication through completion of study;
 - b) Subjects taking antihistamines for minor conditions, such as seasonal rhinitis, may have participated as long as they could safely and comfortably stop the medication for at least two weeks before receiving study medication through completion of study;
 - c) Subjects taking any OTC medication, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), laxatives, stool softeners, vitamins, or herbal supplements, must have discontinued them at least two weeks before receiving study medication and could not resume the medication until the completion of study.
3. Subjects who were taking any Calcium Channel Blockers (e.g. verapamil)
4. Subjects with a history within past 2 years or current substance abuse, either alcohol or other drug/substance, or consumption of more than 2 standard units of alcohol per day (a standard unit equals 12 ounces of beer, 1 1/2 ounces of 80-proof alcohol, or 6 ounces of wine).
5. Subjects with a current or history within one year prior to study entry of tobacco smoking or use of smokeless tobacco (nicotine).
6. Subjects with a known history of Asthma, chronic obstructive pulmonary disease, restrictive lung disease, pulmonary hypertension, clinically significant cardiac arrhythmias, clinically significant cardiac conduction abnormalities.
7. Subject who had symptoms of, or conditions associated with, muscle weakness/disorders and/or scoliosis.
8. Subjects with any acute symptomatic state (e.g. nausea, vomiting, fever, or diarrhea) within 2 weeks before receiving study medication.
9. Subjects with any clinically significant abnormality on any prior ECG or on screening ECG.

10. Subjects with any laboratory abnormality >grade 1 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4 criteria or any grade 1 or ungraded abnormality which, in the opinion of the investigator, was clinically significant.
11. Subjects who had donated blood within 60 days or plasma within 14 days prior to receiving study medication.
12. Subjects who had participated in another interventional clinical trial within 30 days prior to receiving study medication.
13. Subjects who had a positive urine screen for alcohol or drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates) or for cotinine.
14. Subjects who had a positive test for, or had been treated for hepatitis B (HBsAg), hepatitis C (HCV) or human immunodeficiency virus (HIV).
15. Subjects with known hypersensitivity to dantrolene, mannitol, polysorbate-80, povidone, or to iodine.
16. Subjects who had consumed products containing caffeine within 72 hours prior to first dose of study medication.
17. Subjects with a history of recent pneumonia.
18. Subjects with a history or presence of myopathy or neuropathy.
19. Subjects with false nails that may affect pulse oximetry values.
20. Subjects with a Mallampati score greater than 2.
21. Subjects with a shellfish allergy
22. Subjects who had an upper respiratory tract infection within the last 30 days or a recent pneumonia.
23. Subjects with Raynaud syndrome
24. Subjects with Dysautonomia
25. Subjects with thyroid disease
26. Subjects with a history of severe allergic reaction or anaphylaxis associated with any drug.

Summary of Methodology

The Applicant planned to conduct the study in two parts:

1. Dose escalation of single doses of Ryanodex to determine the MTD at various rates of infusion
2. Randomized, single-blind, active controlled, crossover study of single doses of Ryanodex and Dantrium at infusion rates determined from Part 1

Subjects were to have been screened within 4 weeks of the planned date of dosing. Qualified subjects were to have been admitted to the clinical research unit the day prior to dosing (including, initial dosing for subjects participating in the crossover portion of the study). On admission, they were to have undergone repeat evaluation for confirmation of medical history, physical examination and laboratory testing. All subjects were to have remained in the clinical unit through the last blood draw, which

was approximately 72 hours after dosing. Those subjects participating in the crossover part of the study were to have remained in the clinical unit for at least 72 hours after each dose. If clinically fit, subjects were to have been allowed to go home between dosing periods, but were to have returned to the clinical unit the day prior to the second dose.

In Part 1, there were to have been three cohorts. The first cohort was to have had 6 subjects; 4 who received Ryanodex and 2 who received placebo (normal saline). The remaining two cohorts were to have had 5 subjects each; 4 who received Ryanodex and 1 who received placebo. The doses for each of the cohorts are listed in Table 17 below. The study drugs were to have been administered by intravenous (IV) infusion over 30 seconds.

Table 17. Study treatments (planned) for Part 1 (based on Table 1, p. 28 of final study report)

Cohort Number	Dantrolene Sodium Dose Level	Treatment Groups	
		Ryanodex	Placebo
1	1.0 mg/kg	4 subjects	2 subjects
2	1.75 mg/kg	4 subjects	1 subject
3	2.5 mg/kg	4 subjects	1 subject

The maximum tolerated dose (MTD) was defined as follows:

- If a total of two subjects in a cohort in Part 1 of the study experienced a dose-limiting toxicity (DLT), treatment allocation was to be unblinded for those subjects.
- If the subjects who experienced a DLT received active drug, no more subjects would be entered at that or a higher dose, and the previous dose level would be considered the study-specific MTD.
- If two or more of the subjects in a cohort experienced grade 2 toxicity, and no subject experienced a DLT, the Investigator in consultation with the Sponsor would review the data on subjects at that dose level and those of other subjects treated at the previous dose level.
 - If both the Investigator and Sponsor concurred, the dose could be escalated without additional subjects treated at the current dose level.
 - With concurrence between the Investigator and the Sponsor, an additional 4 subjects (3 active/1 placebo) may have been treated at that dose level to further define the toxicity of the dose.
 - Alternatively, if either the Investigator or Sponsor felt that there was a significant probability of severe toxicity or clinically significant acute changes in hepatic, renal or hematological parameters to subjects treated at the next dose level, no further subjects would be enrolled and the current dose level was determined to be the MTD.

The next cohort was not to have been dosed until the safety data from the previous cohort had been reviewed, and the AEs possibly related to study drug had either resolved or it had become evident that no further clinical sequelae would result from the ongoing event.

If two or more subjects developed grade 2 toxicity and none developed a DLT, treatment would be unblinded only if there was a question regarding causality. In this regard, if multiple objective changes that were expected pharmacologic effects of dantrolene occurred in a given subject, it may have been assumed that the affected individual received active drug. If the AEs were subjective and occurred without accompanying expected pharmacologic changes (e.g., severe dyspnea in the absence of substantial change in respiratory muscle strength), or if it was unclear whether the events were related to study medication, treatment for the individual or individuals in question would be unblinded.

The schedules that follow (Table 18, Table 19, Table 20, and Table 21) outline the timing of events for the trial.

Schedules

Table 18. Assessments for subjects in Cohorts 1, 2 and 3 of Part 1 (Table 2, p. 30 of final study report)

Time from START of treatment	PK sampling	P-R-BP ^b	Temp	Pulse oximetry	Head lift	MIP-MEP	Grip strength	12 Lead EKG	Telemetry	Subjective status Likert scales	Questioning re: AEs	Safety Labs	Stair climb
-15 to 0 min	X	X	X	C		X	X		C	X			
1 min	X	X		C					C				
5 min	X	X		C					C	X	X		
15 min	X	X		C	X	X	X	X	C	X	X		
30 min	X	X	X	C					C				
45 min	X			C	X	X	X		C	X	X		
1 h	X	X	X	C				X	C				
1.5 h	X	X	X	C	X	X	X		C	X	X		
2 h	X	X	X	C	X	X	X		C	X	X		
3 h			X	C	X	X	X		C	X			
4 h	X	X	X	C	X	X	X		C	X	X		
6 h	X		X	C	X	X	X		C	X			
8 h	X	X	X	C	X	X	X		C	X	X		
10 h	X		X	C	X	X	X		C	X			
12 h	X	X	X	C					C		X		
24 h	X	X	X	X		X	X	X	C	X	X	X	
36 h	X	X	X	X		X ^a	X ^a			X ^a	X		
48 h	X	X	X	X		X ^a	X ^a			X ^a	X		
72 h	X	X	X	X		X ^a	X ^a	X		X ^a	X	X	X

X = perform test at that time.

C = continuous recording over the period.

^a If not back to ≥90% baseline at previous assessment.

^b If unstable at the end of the initial 12 hr observation period, monitoring should continue as long as clinically indicated.

Table 19. Assessments for subjects in Cohort 3b of Part 1 (Table 3, p. 31 of final study report)

Time from START of treatment	PK sampling	P-R-BP ^b	Temp	Pulse oximetry	Head lift	MIP-MEP	Grip strength	12 Lead EKG	Telemetry	Subjective status Likert scales	Questioning re: AEs	Safety Labs	Stair climb
-15 to 0 min	X	X	X	C		X	X		C	X			
1.5 min	X	X		C					C				
3 min	X			C					C				
6 min	X	X		C					C	X	X		
10 min	X	X		C					C				
15 min				C	X	X	X	X	C	X	X		
20 min	X	X	X	C					C				
40 min	X			C					C				
45min				C	X	X	X		C	X	X		
1 h	X	X	X	C				X	C				
1.5 h	X	X	X	C	X	X	X		C	X	X		
2 h	X	X	X	C	X	X	X		C	X	X		
3 h			X	C	X	X	X		C	X			
4 h	X	X	X	C	X	X	X		C	X	X		
6 h	X		X	C	X	X	X		C	X			
8 h	X	X	X	C	X	X	X		C	X	X		
10 h	X		X	C	X	X	X		C	X			
12 h	X	X	X	C					C		X		
24 h	X	X	X	X		X	X	X	C	X	X	X	
36 h	X	X	X	X		X ^a	X ^a			X ^a	X		
48 h	X	X	X	X		X ^a	X ^a			X ^a	X		
72 h	X	X	X	X		X ^a	X ^a	X		X ^a	X	X	X

X=perform test at that time.

C=continuous recording over the period.

^a If not back to ≥90% baseline at previous assessment.

^b If unstable at the end of the initial 12 hr observation period, monitoring should continue as long as clinically indicated.

Additional monitoring such as EtCO₂, ear pulse oximetry, or other tests, may be incorporated on a case by case basis at the discretion of the Investigator evaluate the safety of subjects.

Table 20. Assessments with 1st dose of Part 2 (based on Table 4, pp. 32-33 of final study report)

Time from END of treatment (1 st dose)	Study day	PK sampling	P-R-BP ^d	Temp	Pulse oximetry	Head lift	Grip strength	MIP-MEP	Subjective status Likert scales	Questioning re: AEs	Safety labs	12-lead ECG	Telemetry	Stair climb
-15 to 0 min	1	X	X	X	C		X	X	X				C	
1 min		X	X		C								C	
5 min		X	X		C				X	X			C	
15 min		X	X		C	X	X	X	X	X		X	C	
29 min		X	X	X	C								C	
35 min		X	X		C								C	
45 min		X			C	X	X	X	X	X			C	
1 h		X	X	X	C							X	C	
1.25 h		X	X		C								C	
1.5 h		X	X	X	C	X	X	X	X	X			C	
2 h		X	X	X	C	X	X	X	X	X			C	
3 h				X	C	X	X	X	X				C	
4 h		X	X	X	C	X	X	X	X	X			C	
6 h		X		X	C	X	X	X	X				C	
8 h		X	X	X	C	X	X	X	X	X			C	
10 h		X		X	C	X	X	X	X				C	
12 h	X	X	X	C					X			C		
24 h	2	X	X	X	X		X	X	X	X	X	X	C ^d	
36 h		X	X	X	X		X ^a	X ^a	X ^a	X				
48 h	3	X	X	X	X		X ^a	X ^a	X ^a	X				
72 h	4	X	X	X	X		X ^a	X ^a	X ^a	X	X	X		X
Minimum 96 hour break														

X=perform test at that time. C=continuous recording over the period.

^a If not back to ≥90% baseline at previous assessment.

^d If unstable at the end of the initial 24 hr observation period, monitoring should continue as long as clinically indicated.

Table 21. Assessments with 2nd dose of Part 2 (based on Table 4, pp. 32-33 of final study report)

Time from END of treatment (2 nd dose)	Study day	PK sampling	P-R-BP ^d	Temp	Pulse oximetry	Head lift	Grip strength	MIP-MEP	Subjective status Likert scales	Questioning re: AEs	Safety labs	12-lead ECG	Telemetry	Stair climb
-15 to 0 min ^b	5 ^c	X	X	X	C		X	X	X				C	
1 min		X	X		C								C	
5 min		X	X		C				X	X			C	
15 min		X	X		C	X	X	X	X	X		X	C	
29 min		X	X	X	C								C	
35 min		X	X		C								C	
45 min		X			C	X	X	X	X	X			C	
1 h		X	X	X	C							X	C	
1.25 h		X	X		C								C	
1.5 h		X	X	X	C	X	X	X	X	X			C	
2 h		X	X	X	C	X	X	X	X	X			C	
3 h				X	C	X	X	X	X				C	
4 h		X	X	X	C	X	X	X	X	X			C	
6 h		X		X	C	X	X	X	X				C	
8 h		X	X	X	C	X	X	X	X	X			C	
10 h		X		X	C	X	X	X	X				C	
12 h	X	X	X	C					X			C		
24 h	6 ^c	X	X	X	X		X	X	X	X	X	X	C ^d	
36 h		X	X	X	X		X ^a	X ^a	X ^a	X				
48 h	7 ^c	X	X	X	X		X ^a	X ^a	X ^a	X				
72 h	8 ^c	X	X	X	X		X ^a	X ^a	X ^a	X	X	X		X

X = perform test at that time.

C = continuous recording over the period.

^a If not back to ≥90% baseline at previous assessment.

^b If a PICC line is used, it should be replaced between the first and second portions of the study to reduce infection risk.

^c study day may vary with break between doses

^d If unstable at the end of the initial 24 hr observation period, monitoring should continue as long as clinically indicated.

Protocol Amendments

The protocol was modified twice.

Amendment 01 (July 27, 2012)

1. Deleted dosing of the initial cohort over two days.
2. Added a third characteristic to the study dose-limiting toxicity (DLT) defined as clinically significant acute changes in hepatic, renal, or hematological parameters.
3. Clarified that the next cohort would not be dosed until safety data from the previous cohort had been reviewed and adverse events possibly related to the study drug have resolved or it is evident that no further clinical sequelae will result from the ongoing event.
4. Added section 5.1.3 Interim Safety Evaluation (24 hours post dose) to include additional safety labs (CBC, biochemical profile, UA, CK, PT/PTT/INR) at 24 hours post dose.
5. Clarified that a CBC, biochemical profile, CK, urinalysis, and PT/PTT/INR (safety labs) will be obtained on all subjects who received any study treatment at 24 hours from the time the dose was delivered.
6. Added safety labs to 24-hour procedures in the procedures for Dose Escalation (Part 1) and (Days 2 and 6) in the procedures for Crossover (Part 2).
7. Clarified that a 12-lead ECG, physical examination, CBC, biochemical profile, CK, urinalysis, and PT/PTT/INR will be obtained on all subjects at 72 hours after each dose administered.
8. Allowed for Medical Monitor to determine that it is safe to proceed with dose escalation.
9. Clarified that Discharge is at 72 hours post dose and deleted telemetry requirement from the 12-Lead ECG testing.
10. Corrected copy and paste error from Dose 1 of Table 3 to Dose 2 of Table 3 (removed head lifting, grip strength, MIP-MEP, Likert scale, and AE questioning from 29 min and 1 hr time points on Day 5; added 12-lead ECG reading to the 1 hour timepoint on Day 5; removed head lifting, grip strength, MIP-MEP, and AE questioning from the 1.25-hour timepoint on Day 5, from Dose 2.
11. Added clarification statements to the description of study procedures for Vital Signs referencing timing per the procedure schedules rather than starting approximately 15 min prior to dosing and continuing for the first 12 hours afterwards and outlining that telemetry will begin approximately 12 hours prior to dose and will continue for 24 hours after dose.
12. Clarified that study is double-blinded in Part 1 for dose escalation single blinded in Part 2 cross-over period.
13. Clarified that Dantrium may be administered by either infusion pump or by manual injection.
14. Clarified that subjects should be either semi-recumbent or sitting upright for MIP/MEP Measurement procedures. Either position is acceptable; it is preferred that the position is consistent through the testing period but will be dependent

upon the clinical condition of the subject. Also clarified that subject should hold the meter in a comfortable manner to perform the test.

Amendment 02 (September 13, 2012):

1. Removed time period of 30 seconds of administration of Ryanodex at 50 mg/mL (push method) to explore extended Ryanodex infusion rates.
2. Added extended Ryanodex infusion rates (from less than 1 minute up to 5 minutes) to generate additional safety data for comparison to Dantrium.
3. Permitted intermediate doses or new dose infusion rates that could be tested in separate special cohorts of up to 10 subjects, to occur between dose escalation levels during Part 1, to refine the MTD and provide additional safety and pharmacokinetic information regarding infusion rates for further dose escalations. During these special cohorts, subjects would be dosed with a single, previously utilized, dose level, but with different infusion rates. The infusion rates utilized will evaluate safety of delivery of the study drug dose over 30 seconds (as described in Part 1 dose escalation) compared with an infusion rate of a dose occurring up to 5 minutes in duration. For dosing during these special cohorts the investigator will be blinded to the subjects' treatments and staff other than pharmacy/nursing staff who actually administer the drug. Dosing of the cohort may be completed over a single or multiple days. Special cohorts will be tested to occur between dose escalation levels during Part 1 to refine the MTD and provide additional safety and PK data regarding infusion rates for further dose escalations.
4. Broadened the allowable dosage of Ryanodex and Dantrium by having total of 12 additional naïve subjects will each receive the maximum tolerated dose of Ryanodex formulation or 2.5 mg/kg dose (whichever is lowest), and an equivalent dose of Dantrium.
5. Required the Dantrium dose to be administered intravenously per MHAUS guidelines and at a rate to best match the Ryanodex dose administration period determined in Part 1 at the extended Ryanodex infusion rate.
6. Added INR to PT/PPT clinical safety laboratory tests.
7. Required the single-dose pharmacokinetic profile of Ryanodex to be conducted at various doses and rates of infusion to expand the safety and PK profile.
8. Required the maximum tolerated single dose (MTD) of Ryanodex to be determined from various doses and rates of infusion of Ryanodex.
9. Clarified that dose escalation of single doses of Ryanodex to determine maximum tolerated dose (MTD) will be conducted at various rates of infusion in Part 1 of the study, and that in Part 2, the infusion rates will be determined from Part 1.
10. Required the Dantrium dose to be administered as close to the same infusion time as possible of Ryanodex as determined in Part 1 of the study and not limited to 15-30 minutes.
11. Added additional special cohort testing and additional PK samples and adjustments to the study to provide safety information for further dose escalation

- which will be determine new infusion after preliminary safety and PK data from first cohorts.
12. Allowed the inclusion in the protocol of a special cohort of subjects to explore extended Ryanodex infusion rates for the purposes of:
 - a. Reducing local or peak concentrations of dantrolene
 - b. Longer infusion rate of Ryanodex could potentially reduce the side effects (AEs) from the local or peak concentrations of dantrolene.
 - c. Generate additional safety data before further dose escalations
 - d. Allows for having a more closely matched time of infusion of Ryanodex compared to Dantrium in Part 2 of the study. By having both Ryanodex and Dantrium infused at the SAME (5 minute) infusion rate will better be able to compare the two study drugs
 13. Added that subjects in special cohorts, who may be dosed at the same dose level but at different infusion rates, will undergo safety evaluations by treatment-blinded staff.
 14. Added that the double blinding of the administered treatments in special cohort testing and Part 2 will be maintained by PK sampling and other scheduled study procedures.
 15. Allowed additional monitoring, such as end tidal CO₂ (EtCO₂), ear pulse oximetry, or other tests, that may be incorporated on a case by case basis at the discretion of the Investigators to evaluate the safety of subjects.
 16. Added procedures to be carried out for all participants in the special cohorts dose escalation part of the study along with additional monitoring to evaluate safety information.

Amendment 1 became effective on July 31, 2012, before any subjects had received study drug. Amendment 2, which only affected subjects in the special cohort, i.e., Cohort 3b, became effective on September 17, 2012, before any subjects in that cohort had been treated with study drug. Thus, neither amendment confounded the safety data collected for either part of the trial.

Protocol Deviations

There were a total of 96 protocol deviations involving 18 subjects. None of these deviations were considered by the applicant to have had any impact on the study outcome; therefore, no data were excluded from their analyses due to the deviations.

A review of the individual deviations indicated the majority were missed assessments, especially drawing of PK blood samples, at the protocol-mandated time points. Other deviations included failure of subjects to consume the appropriate amounts of their meals or fluids. I concur with the Applicant that the deviations are not likely to have a significant impact on the study findings and that all the safety data collected should be included in the analyses.

Subject Disposition

A total of 23 subjects (male and female) were enrolled in the Part 1 of the study and randomized to treatment. A total of 19 subjects received 1 dose of Ryanodex; 5 subjects were treated with placebo. The disposition of these subjects is summarized in Table 22.

Table 22. Disposition of subjects from Part 1 of the study (based on Table 9, p.52 of final study report)

Disposition	1.0 mg/kg Infused over 30 sec (N=4)	1.75 mg/kg Infused over 30 sec (N=9)	1.75 mg/kg Infused over 5 min (N=4)	2.0 mg/kg Infused over 30 sec (N=2)	Placebo Infused over 30 sec (N=4)
Enrolled	4	9	4	2	4
Randomized n (%)	4 (100)	9 (100)	4 (100)	2 (100)	4 (100)
Completed Treatment n (%)	4 (100)	9 (100)	4 (100)	2 (100)	4 (100)
Discontinued	0	0	0	0	0

Reported Safety Results

The demographics for the subjects are summarized in Table 23 below. The population was homogenous across treatment arms for age, weight, and body mass index. There were uneven distributions by gender and race both of which were attributed to the small number of subjects enrolled.

Table 23. Subject demographics (based on Table 10, pp. 53-54 of final study report)

Demographic	1.0 mg/kg Infused over 30 sec (N=4)	1.75 mg/kg Infused over 30 sec (N=9)	1.75 mg/kg Infused over 5 min. (N=4)	2.0 mg/kg Infused over 30 sec (N=2)	Placebo (N=4)
Age (years)					
Mean	30.3	25.7	31.5	29.5	28.8
(SD)	(9.43)	(4.72)	(8.81)	(12.02)	(7.93)
Min	19	21	22	21	21
Max	39	35	42	38	37
Gender					
Female	3 (75)	3 (33)	2 (50)	0	2 (50)
Male	1 (25)	6 (67)	2 (50)	2 (100)	2 (50)
Race n(%)					
American Indian or Alaska Native	0	0	0	1 (50)	1 (25)
Asian	0	1 (11)	0	0	0
Black	2 (50)	0	1 (25)	1 (50)	1 (25)
Native Hawaiian or Pacific Islander	1 (25)	0	0	0	0
White	1 (25)	8 (89)	3 (75)	0	2 (50)

The Applicant summarized the pharmacokinetic findings as follows:

1. Dantrolene and 5-hydroxydantrolene plasma concentrations increased with increasing dose following single dose administration of Ryanodex over the 1.0 to 2.0 mg/kg dose range tested.
2. Higher C_{max} values were evident for Ryanodex 1.75 mg/kg administered as a 30-second bolus compared to Ryanodex 1.75 mg/kg administered as a 5-minute infusion and were consistent with the more rapid dantrolene administration rate of bolus administration.
3. By 72 hours postdose, the majority of the dantrolene and 5-hydroxydantrolene concentrations were below the limit of detection of the assay.
4. Gender differences were not fully evaluated due to the small sample size (8 females and 11 males) and unbalanced study design. However, for both dantrolene and its metabolite, 5-hydroxydantrolene, differences based on gender, between and within dose groups, were not evident.

Subjects were dosed with Ryanodex up to 2.0 mg/kg with no protocol-defined DLTs. There were no SAEs reported and no subject was withdrawn from the study due to a TEAE. The Applicant also noted that there were no laboratory abnormalities that were considered clinically significant and no significant vital sign changes except for one subject, treated with 2 mg/kg of Ryanodex, who experienced transient hypotension.

While most subjects reported at least one AE during the study, the Applicant indicated that most events were generally as expected, were mild to moderate, of short duration and would be easily manageable in a patient with MH.

The following adverse events were noteworthy due to their multiplicity or severity:

1. One subject (1302) at the 2.0 mg/kg dose experienced dizziness, confusion, dyspnea, dysarthria, dysphagia, weakness, somnolence, fatigue and nausea -all (except nausea and fatigue) starting within 5 minutes of dosing. The subject also displayed junctional bradycardia, hypotension, decreased oxygen saturation, and respiratory muscle weakness. The hypotension and respiratory muscle weakness were considered severe in intensity. The hypotension and decreased oxygen saturation required concomitant treatment (oxygen and IV fluid) and resolved rapidly with intervention. Further evaluation regarding this case showed that subject most likely had a vasovagal reaction. The subsequent PK data (very low dantrolene plasma levels at the early postdose time points) and the quick recovery to normal clinical parameters were considered by the Applicant to support the hypothesis that the subject had a vasovagal reaction.
2. Two other subjects, both of whom received 0.5 min infusions of 1.75 mg/kg of Ryanodex, had severe AEs which were considered related to study medication. Per the protocol definition, these could be considered DLTs:
 - a. Subject 1309 had generalized weakness resulting in no sequelae
 - b. Subject 1313 also had generalized weakness resulting in no sequelae.

However, the Applicant indicated that weakness is not only an expected pharmacological effect of dantrolene but was also transient. In a controlled setting, such as the operating room, it should pose no danger.

3. Two subjects (1306 and 1311) who received 1.75 mg/kg Ryanodex (infused over 5 min) had average MIP < 40 cm at one or more time points during the study. However, these results could not be (or were not) duplicated and were not accompanied by clinical symptoms. The Applicant believed this indicated that the results are highly variable and the validity of the test is probably directly related to the quality of the test. Therefore, conclusions regarding the MIP test should only be made in combination with the actual clinical picture and other noninvasive tests such as O₂ saturation and etCO₂ measurements.

The adverse events for the study are summarized in Table 24 below. Based on the adverse events and the laboratory and clinical evaluations, the Applicant drew the following conclusions regarding the safety of Ryanodex:

1. Ryanodex was tolerated at the 1.0 to 2.0 mg/kg doses administered in this study.
2. Some of the events which had originally been defined as dose-limiting needed to be re-evaluated:
 - a. The AEs of severe weakness did not correlate with either grip tests or Likert scale results,
 - b. The marked decreases in absolute value of MIP were not accompanied with signs (increased etCO₂) or symptoms (severe dyspnea or related AEs) consistent with respiratory insufficiency.
3. The inconsistencies in results, assessed by different clinical parameters, indicated that the protocol should be amended to fit the clinical situation rather than continuing the study with specifications which resulted in identification of a clinically incorrect upper dose limit.
4. Amending the protocol to revise the criteria for determining the maximum tolerated dose and to refine the evaluations for weakness and respiratory function would require a new clinical research organization and create difficulties interpreting data gathered prior to and after the amendments. Therefore, it was considered more expeditious to terminate the trial prematurely, revise the protocol, and begin the trial anew.

Table 24. Summary adverse events (based on Table 14, pp. 75–78 of final study report)

System Organ Class Preferred Term	1.0 mg/kg Infused over 30 sec (N=4)	1.75 mg/kg Infused over 30 sec (N=9)	1.75 mg/kg Infused over 5 min. (N=4)	2.0 mg/kg Infused over 30 sec (N=2)	Placebo (N=4)
Number of Subjects with at least 1 Treatment Emergent Adverse Event	4 (100)	9 (100)	4 (100)	2 (100)	2 (50)
Cardiac disorders	1 (25)	2 (22)	1 (25)	2 (100)	0
Bradycardia	0	1 (11)	0	0	0
Nodal arrhythmia	0	0	0	1 (50)	0
Palpitations	0	2 (22)	1 (25)	0	0
Sinus tachycardia	1 (25)	0	0	1 (50)	0
Tachycardia	0	1 (11)	0	0	0
Ear and labyrinth disorders	0	0	1 (25)	0	0
Eye disorders	0	2 (22)	2 (50)	0	0
Diplopia	0	1 (11)	1 (25)	0	0
Vision blurred	0	2 (22)	2 (50)	0	0
Gastrointestinal disorders	1 (25)	7 (78)	3 (75)	1 (50)	1 (25)
Dysphagia	0	6 (67)	1 (25)	1 (50)	0
Nausea	1 (25)	4 (44)	2 (50)	1 (50)	1 (25)
General disorders and administration site conditions	3 (75)	9 (100)	3 (75)	2 (100)	1 (25)
Asthenia	2 (50)	9 (100)	3 (75)	2 (100)	0
Fatigue	3 (75)	5 (56)	3 (75)	2 (100)	0
Feeling hot	1 (25)	2 (22)	1 (25)	0	0
Infusion site pain	2 (50)	0	0	0	0
Inspiratory capacity decreased	0	0	2 (50)	0	0
Oxygen saturation decreased	0	0	0	1 (50)	0
Musculoskeletal and connective tissue disorders	2 (50)	4 (44)	2 (50)	0	0
Muscle spasms	0	1 (11)	0	0	0
Muscular weakness	1 (25)	2 (22)	1 (25)	0	0
Nervous system disorders	3 (75)	9 (100)	4 (100)	2 (100)	2 (50)
Dizziness	2 (50)	9 (100)	3 (75)	2 (100)	1 (25)
Dysarthria	0	5 (56)	0	1 (50)	0
Muscle contractions involuntary	0	2 (22)	0	0	0
Paraesthesia	0	2 (22)	0	0	1 (25)
Somnolence	2 (50)	5 (56)	2 (50)	1 (50)	0

System Organ Class Preferred Term	1.0 mg/kg Infused over 30 sec (N=4)	1.75 mg/kg Infused over 30 sec (N=9)	1.75 mg/kg Infused over 5 min. (N=4)	2.0 mg/kg Infused over 30 sec (N=2)	Placebo (N=4)
Psychiatric disorders	1 (25)	3 (33)	3 (75)	1 (50)	0
Renal and urinary disorders	0	1 (11)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	4 (44)	2 (50)	2 (100)	0
Dyspnoea	0	4 (44)	2 (50)	2 (100)	0
Respiratory muscle weakness	0	0	0	1 (50)	0
Skin and subcutaneous tissue disorders	1 (25)	1 (11)	0	0	0
Vascular disorders	0	0	1 (25)	1 (50)	0
Flushing	0	0	1 (25)	0	0
Hypotension	0	0	0	1 (50)	0

Discussion

Overall, the safety data suggest that Ryanodex has an adverse event profile similar to that reported for Dantrium. The numbers of subjects in each of the dose groups were too small to allow an assessment of dose dependency. Similarly, the number of subjects evaluated with the 5-minute infusion of 1.75 mg/kg of Ryanodex was too small to make a meaningful comparison of the safety profile with that for subjects who received the same dose over 30 seconds.

The study was halted after detailed evaluation of events at the 1.75 mg/kg and 2.0 mg/kg doses was completed and the protocol was modified to allow for assessments of adverse events that the Applicant thought would be more “accurate.” These changes were incorporated into Amendment 3, which was dated December 6, 2012, after Trial 1201A was terminated and prior to initiation of Trial 1201. Amendment 03 changed the study as follows:

- Incorporated Dantrium dosing at all dose levels, in parallel and as a double blinded treatment, with Ryanodex in order to permit the objective comparison of Ryanodex vs. Dantrium (treatment effects) at all doses given.
- Added continuous hemodynamic monitoring and ABG tests as safety measurements for determining respiratory insufficiency as a dose limiting toxicity which made for more objective criteria of respiratory failure and because arterial waveform was available for real-time hemodynamic monitoring to assure subject safety during rapid drug-related transitions.
- Removed maximum inspiratory pressure (MIP) from dose limiting toxicity criteria as MIP is highly variable and a subject effort-dependent measure; while there are known neurological/psychological effects of dantrolene that may alter test

results/compliance, the applicability of MIP to respiratory failure has not been validated.

- Subjects were dosed supine, and assessed in the supine position because this position stabilizes hemodynamics and minimizes vasovagal syncope response and because therapeutic doses are typically delivered to supine patients.
- Specified Ryanodex administration over 1 minute.
- Specified Dantrium administration at 50 mL/min infusion rate.
- Specified both drug administration procedures to be given in a double-blind fashion to protect the objective evaluation of the subject.

As the clinical research organization (CRO) did not have the capability to continue the study with the additional testing required by Amendment 03, the study was moved to a new CRO and restarted at the 1.0 mg/kg dose.

Conclusions

Although the study was terminated prematurely, it generated useful PK data for Ryanodex and its 5-hydroxydantrolene metabolite. It also generated some useful, if preliminary, safety data, which indicated the product has a safety profile not dissimilar to that of the approved formulation, Dantrium. Some of the safety issues which raise the greatest concern for patients' well-being are not generally of concern in the setting where Ryanodex will be used most frequently, i.e., the operating room while the patients are unconscious, intubated, and mechanically ventilated. In this setting, muscle weakness, decreased respiratory capacity, somnolence, dizziness, dysphagia, and nausea will not likely pose substantial, if any, risks to the patient. The use of Ryanodex either preoperatively for prophylaxis against MH or following an episode of MH to prevent recrudescence, may be associated with increased risk when administered to conscious patients. However, these patients are in a setting where they can easily be monitored for the more common adverse reactions and readily treated if the reactions are severe enough to warrant intervention.

The decision by the Applicant to terminate the trial prematurely and restart it with the proposed modifications to the protocol was appropriate given the findings of Trial 1201A at the time of the interim analysis and the types of changes to the protocol made with amendment 3.

9.4.2 EGL-Dantrolene-1201

Title: Pharmacokinetics and Safety of Dantrolene Sodium Suspension (Ryanodex®) compared to Dantrolene Sodium for Injection (Dantrium® Intravenous) in Healthy Volunteers

Dates: December 20, 2012 through February 24, 2013

Objectives

Primary:

To characterize the single dose pharmacokinetic profile of Ryanodex in conscious healthy volunteers

Secondary:

- To determine the maximum tolerated dose (MTD) of Ryanodex and/or Dantrium for comparison in conscious healthy volunteers for purposes of the crossover comparison
- To compare the single-dose pharmacokinetic profile and evaluate the safety and tolerability of Ryanodex and Dantrium in conscious healthy volunteers

Endpoints

Efficacy:

No efficacy endpoints were evaluated in this study.

Safety and Tolerability:

- Maximum tolerated dose (MTD): determined based on the occurrence of dose-limiting toxicities, as defined in the protocol. In the absence of dose-limiting toxicities, grade 2 toxicities were considered in determining the MTD.
- Adverse Events
- Physical Examinations: including general appearance, head, eyes, ears, nose, throat (HEENT), thyroid (endocrine), heart, chest, lungs, abdomen, skin, neurological, extremities, and back
- Vital Signs: blood pressure, respiration rate, pulse, oxygen saturation, and temperature
- Laboratory Tests: including full chemistry profile, complete blood count (CBC), urinalysis, coagulation parameters. The NCI-CTCAE Version 4.0 system was used to grade new or worsening laboratory abnormalities. New laboratory abnormalities for which there were no CTCAE Version 4.0 criteria were assigned grade 1 if there were no clinical effects or interventions

- Strength Assessments: Handgrip strength and maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP)
- ECG and telemetry
- Arterial Blood Gases

Pharmacokinetics:

The following parameters were evaluated for plasma dantrolene and 5-hydroxydantrolene: C_{max} , T_{max} , $t_{1/2}$, AUC_{0-24} , AUC_{0-last} , AUC_{0-inf} , Cl_p , V_z , V_{dss} , λ_z , and AUMC (dantrolene only).

Inclusion Criteria (verbatim, pp. 32-33 of final study report)

1. Be male to be enrolled in Part 1. Male and female subjects were allowed in Part 2.
2. If female and of childbearing potential, have agreed to use an effective form of contraception, such as oral or systemic contraception, a diaphragm and spermicide, intrauterine device (IUD), or condom and spermicide used by partner, during the study and for at least one month after its completion.
 - a) For females to be considered of non-childbearing potential due to menopause, the onset of menopause must have been at least one year prior to study entry. Females that were surgically sterile were eligible to participate.
3. If male, have used an effective form of contraception, such as a condom and spermicide or a diaphragm or IUD used by partner, during and for at least one month after completion of study.
4. If female, must have been nonpregnant and nonlactating.
5. Be between the ages of 18 to 45 years, inclusive, at study entry.
6. Have had a BMI between 18-30 kg/m², inclusive.
7. Have had a minimum body weight 50 kg (110 lbs); maximum 100 kg (220 lbs).
8. Have been healthy as determined by the Investigator based on history, physical examination, clinical laboratory tests and 12-lead ECG.
9. Have had adequate radial artery(ies) for catheterization, and sufficient ulnar artery (collateral circulation) to supply the hand with radial artery occlusion test.
10. Have had adequate venous patency in both arms to allow infusion of the planned dose of Ryanodex in less than 60 seconds, and Dantrium infused at 50 mL/min, and to allow venous blood sampling, as determined by the Investigator at examination.
11. Have agreed to abstain from alcohol consumption for 1 week prior to receiving study medication and for the duration of the study.
12. Have been willing and able to remain in the study unit for the entire duration of each confinement period and to return for scheduled follow-up visits.
13. Have been adequately fluent in the English language to provide informed consent, and answer the Likert scale questions.
14. Have provided voluntary written informed consent for participation.

15. Have had normal lung function, defined as forced vital capacity (FVC) \geq 80%, forced expiratory volume (FEV1) \geq 80%, and forced expiratory flow (FEF) 25-75 \geq 65% of predicted normal at screening. Spirometry was performed as per American Thoracic Society (ATS) guidelines.
16. Have demonstrated, in the opinion of the Investigator, a high probability of safely completing the study.

Exclusion Criteria (verbatim, pp. 33-35 of final study report)

1. Subjects with any current or history of any clinically significant medical condition, such as cardiovascular, pulmonary, endocrine, muscular, gastrointestinal, hepatic or psychiatric disorders, which might have, in the opinion of the Investigator, jeopardized the safety of the subject or affected the validity of study results.
2. Subjects who had used any prescription medication (including dantrolene sodium) within 14 days prior to test drug administration
3. Subjects who were taking any over-the-counter (OTC) medication, chronically, intermittently or short-term for any condition, within 7 days prior to test drug administration, including the following:
 - a) Subjects taking prophylactic aspirin may have participated as long as they never had any cardiovascular signs or symptoms, had no evidence of cardiovascular disease and could safely stop the medication(s) for at least one week before receiving study medication through completion of study;
 - b) Subjects taking antihistamines for minor conditions, such as seasonal rhinitis, may have participated as long as they could safely and comfortably stop the medication for at least one week before receiving study medication through completion of study;
 - c) Subjects taking any OTC medication, such as acetaminophen, non-steroidal anti-inflammatories (NSAID), laxatives, stool softeners, vitamins, or herbal supplements, must have discontinued them at least one week before receiving study medication and could not resume the medication until the completion of study.
4. Subjects who took any hepatic (i.e., CYP3A4) metabolism inducers/inhibitors within 28 days prior to test drug administration.
5. Subjects who took any calcium channel blockers (e.g. verapamil).
6. Subjects with a history within past 2 years or current substance abuse, either alcohol or other drug/substance or a positive alcohol or urine drug screen at screening or Day -1.
7. Subjects with a current or history within one year prior to study entry of tobacco smoking or use of smokeless tobacco (nicotine), or subjects with a positive cotinine test at screening or Day -1.
8. Subjects with a known history of clinically significant asthma, chronic obstructive pulmonary disease, restrictive lung disease, pulmonary hypertension, clinically significant cardiac arrhythmias, or clinically significant cardiac conduction abnormalities.

9. Subject who had symptoms of, or conditions associated with, muscle weakness/disorders and/or scoliosis.
10. Subjects with any acute symptomatic state (e.g., nausea, vomiting, fever, or diarrhea) within 2 weeks before receiving study medication.
11. Subjects with any known clinically significant abnormality on prior ECGs, or on screening ECGs.
12. Subjects with any laboratory abnormality >Grade 1 per NCI CTCAE Version 4.0 criteria or any grade 1 or ungraded abnormality which, in the opinion of the Investigator, was clinically significant.
13. Subjects who had donated blood within 60 days or plasma within 14 days prior to receiving study medication.
14. Subjects who had participated in another interventional clinical trial within 30 days prior to receiving study medication.
15. Subjects who had a positive urine screen for alcohol or drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids (including THC), and opiates).
16. Subjects who had a positive test for, or had been treated for hepatitis B, hepatitis C or HIV.
17. Subjects with known hypersensitivity to dantrolene, mannitol, polysorbate-80, povidone, or iodine.
18. Subjects who have consumed products containing caffeine within 72 hours prior to first dose of study medication, at the Investigator's discretion.
19. Subjects with a history of recent pneumonia.
20. Subjects with a history or presence of myopathy or neuropathy.
21. Subjects with false nails that may affect pulse oximetry values.
22. Subjects with a Mallampati score greater than 2.
23. Subjects with a shellfish allergy
24. Subjects who had had an upper respiratory tract infection (URI) within the last 30 days or a recent pneumonia (6 months).
25. Subjects with Raynaud syndrome
26. Subjects with dysautonomia
27. Subjects with thyroid disease
28. Subjects with a history of severe allergic reaction or anaphylaxis associated with any drug.
29. Subjects who had participated in strenuous exercise within 1 week of dose administration.

Summary of Methodology

This trial was divided into two parts and was conducted at a single study center. Part 1 of the trial was a dose-escalation study that involved increasing doses of Ryanodex and Dantrium administered to cohorts of subjects until the maximum tolerated dose (MTD) or the dose of 2.5 mg/kg was reached. Part 2 of the trial was safety and PK study that used a randomized crossover design for administering Ryanodex and Dantrium at the

2.5 mg/kg dose level or at the MTD of Ryanodex or Dantrium achieved in Part 1 of the study, if the MTD was lower than 2.5 mg/kg.

For both parts of the trial, pre-study screening for eligibility occurred up to 30 days before the first dose of study drug. Subjects were admitted to the Clinical Research Unit (CRU) the day before dosing (Day-1). Ryanodex or Dantrium was administered in the morning (Day 0) after an overnight fast. Subjects remained in the CRU for 72 hours after dosing for safety and PK assessments. A follow-up telephone call was made to each subject at 1-2 weeks after dosing. Blood samples for plasma concentrations of dantrolene and its metabolite, 5-hydroxydantrolene, were collected from subjects in Parts 1 and 2 at just prior to dosing (-45 to 0 min), immediately after dosing, 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes; and 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours after dosing.

In Part 1 (single dose escalation), 5 cohorts of 8 healthy male subjects were to have been randomized for administration of either a 1-minute infusion of Ryanodex or a 50 mL/min infusion of Dantrium at the following dose levels:

- 1 mg/kg
- 1.75 mg/kg
- 2 mg/kg
- 2.25 mg/kg
- 2.5 mg/kg

There were to have been 4 subjects exposed to Ryanodex and 4 subjects exposed to Dantrium for each dose group. Treatment groups of Dantrium and Ryanodex administered at the same dose level were to have been conducted in parallel with equal numbers of subjects studied on a single day for blinded comparison. An assessment was to have been made after each dose group to determine whether the MTD had been reached before proceeding with the next dose group.

The following DLT criteria were to have been used in defining the MTD and were based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria:

1. Any grade 3 or 4 toxicity posing a danger to the wellbeing of the subject.
2. Type 2 respiratory failure determined by ABGs, requiring mechanical ventilation.
3. Clinically significant acute changes in hepatic, renal or hematological parameters which pose a danger to the wellbeing of the subject.

If two or more subjects in either treatment group experienced a DLT, no additional subjects were to be treated at that dose level and the previous dose level would be declared as the MTD. Optional testing of both treatment groups at a dose less than the DLT but greater than the prior MTD was to have been at the discretion of the Investigator and Sponsor.

In Part 2 of the trial, 15 healthy male and female subjects were to have received 2.5 mg/kg doses of Ryanodex and Dantrium in a crossover design. The two doses were to have been administered at least 4 days apart, to allow a period of at least 8 half-lives between administrations.

The schedules of assessments for both parts of the studies are provided in Table 25, Table 26, and Table 27 below.

Schedules

Table 25. Evaluations at screening, check in, and discharge (Table 9-2, p. 27 of final study report)

Visit	Informed Consent	Physical Exam	Vital Signs	Pulse oximetry (O2 Sat)	Ht and Wt	Medication History	Safety Labs, PT/PTT	HCV, HBsAg, HIV serologies	Pregnancy test	Urine for drugs of abuse	12 Lead EKG	Grip strength	Calf raises	MIP/MEP	Spirometry	Telemetry	Subjective status Likert scales	Stair climb
Screening	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Check In		X*	X	X		X	X		X	X	X	X	X	X		X**	X	
Discharge		X*	X	X		X	X		X		X	X	X	X				X

* Interim (abbreviated)

** Continuous from 12 hours prior to dose

Table 26. Procedures for Part 1 - dose escalation (Table 9-3, p. 28 of final study report)

Time from END of treatment	PK sampling ^d	P-R-Bp ^b	Temp	Arterial Line BP	ABG	Pulse oximetry	Head lift	MIP/MEP	Calf Raises	Grip strength	12 Lead EKG	Telemetry	Subjective status Likert scales	Questioning regarding AEs	Safety Labs PT/PTT	Stair climb
-45 to 0 min	X	X	X	C	X	C		X		X		C	X			
Immediately after dose	X															
1 min	X	X ^c		C		C						C				
5 min	X	X ^c		C	X	C	X					C	X	X		
15 min	X	X ^c		C		C	X	X		X	X	C	X	X		
20 min		X ^c		C	X	C						C				
30 min	X	X ^c	X	C		C	X	X				C				
45 min	X	X ^c		C		C	X			X		C	X	X		
1 h	X	X ^c	X	C	X	C	X	X			X	C				
1.5 h	X	X ^c	X	C		C				X		C	X	X		
2 h	X	X ^c	X	C		C		X		X		C	X	X		
3 h		X	X			C				X		C	X			
4 h	X	X	X			C		X	X	X		C	X	X		
6 h	X		X			C				X		C	X			
8 h	X	X	X			C		X	X	X		C	X	X		
10 h	X		X			C		X		X		C	X			
12 h	X	X	X			C				X		C		X		
24 h	X	X	X			X		X ^a	X	X	X	C	X	X	X	X
36 h	X	X	X			X		X ^a		X ^a			X ^a	X		
48 h	X	X	X			X		X ^a		X ^a			X ^a	X		
72 h	X	X	X			X				X ^a	X		X ^a	X	X	X

X=perform test at that time. C=continuous recording over the period.

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^a If not back to $\geq 90\%$ baseline at previous assessment.

^b If unstable at the end of the initial 12 hr observation period, monitoring continued as long as clinically indicated.

^c Only pulse and respiration were collected at these indicated time points

^d PK allowable windows were: ± 1 minute for Immediately after Dose to 2 hours; ± 5 minute for 3 hours to 72 hours

Table 27. Procedures for Part 2 – cross over (Table 9-4, pp. 29-31 of final study report)

Time from END of treatment	Dose	PK sampling ^d	P-R-BP ^b	Temp	Arterial Line BP	ABG	Pulse oximetry	Head lift	MIP/MEP	Calf Raises	Grip strength	12 Lead EKG	Telemetry	Subjective status Likert scales	Questioning regarding AEs	Safety Labs, PT/PTT	Stair climb	
Period 1																		
-45 to 0 min	Dose 1	X	X	X	C	X	C		X		X		C	X				
Immediately after dose		X																
1 min		X	X ^c			C		C						C				
5 min		X	X ^c			C	X	C	X					C	X	X		
15 min		X	X ^c			C		C	X	X		X	X	C	X	X		
20 min			X ^c			C	X	C						C				
30 min		X	X _c	X		C		C	X	X				C				
45 min		X	X ^c			C		C	X			X		C	X	X		
1 h		X	X ^c	X		C	X	C	X	X			X	C				
1.5 h		X	X ^c	X		C		C				X		C	X	X		
2 h		X	X ^c	X		C		C		X		X		C	X	X		
3 h			X	X				C				X		C	X			
4 h		X	X	X				C		X	X	X		C	X	X		
6 h		X		X				C				X		C	X			
8 h		X	X	X				C		X	X	X		C	X	X		
10 h		X		X				C		X		X		C	X			
12 h		X	X	X				C				X		C		X		
24 h		X	X	X				X		X ^a	X	X	X	C	X	X	X	X
36 h	X	X	X				X		X ^a		X ^a			X ^a	X			

Time from END of treatment	Dose	PK sampling ^d	P-R-BP ^b	Temp	Arterial Line BP	ABG	Pulse oximetry	Head lift	MIP/MEP	Calf Raises	Grip strength	12 Lead EKG	Telemetry	Subjective status Likert scales	Questioning regarding AEs	Safety Labs, PT/PTT	Stair climb	
48 h		X	X	X			X		X ^a		X ^a			X ^a	X			
72 h		X	X	X			X				X ^a	X		X ^a	X	X	X	
Minimum of 96 hours from 1 st dose																		
Period 2																		
-45 to 0 min	Dose 2	X	X	X	C	X	C		X		X		C	X				
Immediately after dose		X																
1 min		X	X ^c		C		C							C				
5 min		X	X ^c		C	X	C	X						C	X	X		
15 min		X	X ^c		C		C	X	X			X	X	C	X	X		
20 min			X ^c		C	X	C							C				
30 min		X	X ^c	X	C		C	X	X					C				
45 min		X	X ^c		C		C	X				X		C	X	X		
1 h		X	X ^c	X	C	X	C	X	X				X	C				
1.5 h		X	X ^c	X	C		C					X		C	X	X		
2 h		X	X ^c	X	C		C			X		X		C	X	X		
3 h			X	X			C					X		C	X			
4 h		X	X	X			C			X	X	X		C	X	X		
6 h		X		X			C					X		C	X			
8 h	X	X	X			C			X	X	X		C	X	X			
10 h	X		X			C			X		X		C	X				
12 h	X	X	X			C					X		C		X			

Time from END of treatment	Dose	PK sampling ^d	P-R-BP ^b	Temp	Arterial Line BP	ABG	Pulse oximetry	Head lift	MIP/MEP	Calf Raises	Grip strength	12 Lead EKG	Telemetry	Subjective status Likert scales	Questioning regarding AEs	Safety Labs, PT/PTT	Stair climb
24 h	Dose 2																
36 h		X	X	X			X		X ^a		X ^a			X ^a	X		
48 h		X	X	X			X		X ^a		X ^a			X ^a	X		
72 h		X	X	X			X				X ^a	X		X ^a	X	X	X

X=perform test at that time.

C=continuous recording over the period.

^a If not back to ≥90% baseline at previous assessment.

^b If unstable at the end of the initial 12 hr observation period, monitoring continued as long as clinically indicated.

^c Only pulse and respiration were collected at these indicated time points

^d PK allowable windows were: +/- 1 minute for Immediately after Dose to 2 hours; +/- 5 minute for 3 hours to 72 hours

^e In the event that it was not possible to insert an arterial line in Period 2, cuff blood pressure was taken also taken in addition to the arterial line BP.

Protocol Amendments

The protocol was amended once. Amendment 4 became effective on February 1, 2013, prior to any subjects being enrolled in Part 2 of the trial and incorporated the following changes into the protocol:

- Allowed subjects in dose groups from 2.0 to 2.5 mg/kg dose levels to be eligible for participation in the cross-over dose in Part 2 of the study
- Subjects eligible for the crossover portion of the study were given the option of not having an arterial line for dosing in Period 2 (at second dantrolene treatment)
- Eight additional subjects (including females), not enrolled in dose escalation, were added for Part 2 allowing up to 16 total subjects to complete Periods 1 and 2 (Of Part 2) for the crossover portion of the study.

There were no changes made to the Planned analysis prior to unblinding.

Subject Disposition

A total of 38 subjects were enrolled in the study. All subjects who were enrolled received treatment with study drug and completed the study. The distribution of subjects by dose group and their disposition are described in Table 28 below.

Table 28. Subject Disposition (Based on Table 10-8, p. 51 of final study report)

Disposition	1.0 mg/kg		1.75 mg/kg		2.0 mg/kg		2.25 mg/kg		2.5 mg/kg		Total N=38
	A N=3	B N=3	A N=4	B N=4	A N=4	B N=4	A N=4	B N=4	A N=4	B N=4	
Subjects Enrolled in Study	3	3	4	4	4	4	4	4	4	4	38
Subjects Completed n (%)	3 (100)	3 (100)	4 (100)	38 (100)							
Subjects Discontinued n	0	0	0	0	0	0	0	0	0	0	0

A=Ryanodex treatment group; B=Dantrium treatment group

Protocol Deviations

The Applicant reported a total of 109 protocol deviations. The majority of these (63 incidents) were related to grip strength testing in which the non-dominant, i.e., the weaker, hand was used due to either the presence of the arterial line in the dominant wrist or “staff oversight.” The other deviations included the following:

- PK sampling performed at the wrong time (27 incidents) most of which involved a sample collected within 15 minutes of the scheduled time. Actual sample times were used for determination of PK parameters.
- Calf raising assessments performed at the wrong time or not at all (15 incidents).
- Failure to assess blood pressure, oral temperature, maximum inspiratory pressure, and PT/PTT (1 incident each) at the correct time or at all.

The Applicant was asked to summarize the grip strength testing deviations to allow an assessment of the impact they would have the study results. The following two tables, Table 29 and Table 30, summarize the deviations. The data in Table 29 indicate that errors in baseline measurements occurred equally between treatment groups; however, the correction to assessments of grip strengths in the stronger hand for subsequent assessments occurred more frequently with Ryanodex (9 times) compared to Dantrium (3 times). This difference could make Ryanodex appear less likely to affect grip strength than Dantrium.

Table 29. Summary information regarding deviations in grip strength testing (based on table in submission of 03/18/2014 [SDN 005])

DEVIATION: WEAKEST HAND ERRONEOUSLY TESTED ON DAY - 1			
RAND NO	UNIQUE SUBJECT ID	STUDY TREATMENT	DEVIATION CONSISTENTLY APPLIED BEFORE AND AFTER TREATMENT
1003	EGL-DANTROLENE-1201-001-0001	RYANODEX	YES
1004	EGL-DANTROLENE-1201-001-0013	DANTRIUM	YES
1005	EGL-DANTROLENE-1201-001-0020	DANTRIUM	YES
2004	EGL-DANTROLENE-1201-001-0044	DANTRIUM	YES
3001	EGL-DANTROLENE-1201-001-0073	RYANODEX	NO. CORRECTED TO STRONGEST HAND
3002	EGL-DANTROLENE-1201-001-0053	DANTRIUM	YES
3004	EGL-DANTROLENE-1201-001-0076	DANTRIUM	YES
3005	EGL-DANTROLENE-1201-001-0062	RYANODEX	NO. CORRECTED TO STRONGEST HAND
3006	EGL-DANTROLENE-1201-001-0051	DANTRIUM	NO. CORRECTED TO STRONGEST HAND
3007	EGL-DANTROLENE-1201-001-0064	RYANODEX	NO. CORRECTED TO STRONGEST HAND
4002	EGL-DANTROLENE-1201-001-0056	RYANODEX	NO. CORRECTED TO STRONGEST HAND
4003	EGL-DANTROLENE-1201-001-0085	RYANODEX	NO. CORRECTED TO STRONGEST HAND
4004	EGL-DANTROLENE-1201-001-0079	DANTRIUM	NO. CORRECTED TO STRONGEST HAND
4006	EGL-DANTROLENE-1201-001-0072	RYANODEX	NO. CORRECTED TO STRONGEST HAND
4007	EGL-DANTROLENE-1201-001-0080	RYANODEX	NO. CORRECTED TO STRONGEST HAND

DEVIATION: WEAKEST HAND ERRONEOUSLY TESTED ON DAY - 1			
RAND NO	UNIQUE SUBJECT ID	STUDY TREATMENT	DEVIATION CONSISTENTLY APPLIED BEFORE AND AFTER TREATMENT
4008	EGL-DANTROLENE-1201-001-0030	DANTRIUM	YES
5002	EGL-DANTROLENE-1201-001-0091	DANTRIUM	YES
5008	EGL-DANTROLENE-1201-001-0065	RYANODEX, DANTRIUM	NO. CORRECTED FOR DOSE A
6003	EGL-DANTROLENE-1201-001-0108	RYANODEX, DANTRIUM	YES
6004	EGL-DANTROLENE-1201-001-0099	RYANODEX	NO. CORRECTED TO STRONGEST HAND
6008	EGL-DANTROLENE-1201-001-0100	RYANODEX, DANTRIUM	YES

Table 30. Summary information regarding deviations in grip strength testing (based on table in submission of 03/18/2014 [SDN 005])

DEVIATION: WEAKEST HAND BECAUSE OF ARTERIAL LINE PLACEMENT			
RAND NO	UNIQUE SUBJECT ID	STUDY TREATMENT	DEVIATION CONSISTENTLY APPLIED BEFORE AND AFTER TREATMENT
1001	EGL-DANTROLENE-1201-001-0016	RYANODEX	YES
1003	EGL-DANTROLENE-1201-001-0001	RYANODEX	YES
1004	EGL-DANTROLENE-1201-001-0013	DANTRIUM	YES
1005	EGL-DANTROLENE-1201-001-0020	DANTRIUM	YES
2003	EGL-DANTROLENE-1201-001-0041	RYANODEX	YES
2004	EGL-DANTROLENE-1201-001-0044	DANTRIUM	YES
2007	EGL-DANTROLENE-1201-001-0050	RYANODEX	YES
2008	EGL-DANTROLENE-1201-001-0042	DANTRIUM	YES
3002	EGL-DANTROLENE-1201-001-0053	DANTRIUM	YES
3004	EGL-DANTROLENE-1201-001-0076	DANTRIUM	YES
3008	EGL-DANTROLENE-1201-001-0066	DANTRIUM	YES
4005	EGL-DANTROLENE-1201-001-0081	DANTRIUM	YES
4008	EGL-DANTROLENE-1201-001-0030	DANTRIUM	YES
5002	EGL-DANTROLENE-1201-001-0091	DANTRIUM	YES
5003	EGL-DANTROLENE-1201-001-0094	RYANODEX	YES
5008	EGL-DANTROLENE-1201-001-0065	DANTRIUM	YES
6003	EGL-DANTROLENE-1201-001-0108	RYANODEX, DANTRIUM	YES
6004	EGL-DANTROLENE-1201-001-0099	DANTRIUM	YES
6008	EGL-DANTROLENE-1201-001-0100	RYANODEX, DANTRIUM	YES

Reported Results

The Applicant made the following conclusions regarding the pharmacokinetics data collected in this study:

1. Dantrolene and 5-hydroxydantrolene plasma concentrations increased with increasing dose following single dose administration of Ryanodex and Dantrium over the 1.0 mg/kg to 2.5 mg/kg dose range tested. Higher C_{max} values were evident for Ryanodex (relative to Dantrium) and are consistent with the more rapid administration rate of Ryanodex.
2. For each Ryanodex dose investigated (1.0 mg/kg to 2.5 mg/kg), systemic exposure based on AUC for the dantrolene and 5-hydroxydantrolene are comparable to the reference listed drug, Dantrium.
3. The relative bioavailability assessment demonstrated that at the 2.5 mg/kg dose dantrolene AUC_{inf} and C_{max} were 6% and 44% higher for Ryanodex as compared to Dantrium based on the GMR. The 90% confidence intervals (CI) demonstrated that the two treatments were equivalent based on AUC_{inf} . Significant differences between treatments were evident for C_{max} as the 90% CI was 1.18-1.75. For 5-hydroxydantrolene, AUC_{inf} and C_{max} estimates were comparable between the two treatments as the 90% CIs were within the 80-125% equivalence limits.
4. Dose proportionality is evident for both treatments over the doses of 1.0 mg/kg to 2.5 mg/kg for dantrolene C_{max} and 5-hydroxydantrolene C_{max} and AUC_{inf} as the 95% confidence intervals for the slope term, β , contains 1. A slight deviation from dose proportionality is evident for dantrolene AUC_{inf} for both treatments as the lower limit of the 95% confidence intervals were greater than 1, indicating dantrolene exposure was slightly greater than proportional to the dose administered.
5. Based on graphical comparisons, the concentrations of dantrolene and 5-hydroxydantrolene appear to be slightly higher in females when compared to males.

The Applicant reported the following findings related to the safety assessments made during the trial:

1. There were no severe adverse events, SAEs or deaths in the study. No subjects were withdrawn from the study due to an adverse event.
2. Subjects were safely dosed up to 2.5 mg/kg in Part 1 of the study and no dose limiting toxicities occurred.
3. In Part 2 of the study 11 subjects (73%) reported AEs while receiving Ryanodex and 9 subjects (56%) did so when receiving Dantrium. Most of this difference was due to the following AEs:
 - a. Flushing (7 subjects receiving Ryanodex, 1 subject receiving Dantrium)
 - b. Dysphonia (4 Ryanodex vs. 1 Dantrium)
 - c. Dysphagia (3 Ryanodex vs. 1 Dantrium)
4. In all dose groups, adverse events were generally as expected (based on AEs reported in the Dantrium label), were mild to moderate and of short duration.

5. The only notable mean changes from baseline in laboratory safety tests were in CPK which declined over the course of the study equally in both treatment groups and was expected given the action of the study drug and the confinement (i.e. low exertion) of the subjects during the study. Otherwise, mean changes from baseline in hematology, chemistry, coagulation, and urinalysis values were generally small and considered not clinically meaningful.
6. There were no clinical meaningful changes in vital signs or ECGs during the study.
7. Hand grip strength diminished very quickly after dosing in all dose groups treated in the study.
8. In the 2.5 mg/kg treatment group the decline in hand grip strength both in amount and duration was nearly identical between the two treatment groups (Ryanodex vs. Dantrium).
9. Subjective status assessments (Likert Scale) indicated fatigue and weakness from 5 minutes postdose and continuing for about 24 hours postdose in all treatment groups except the lowest dose. There were no apparent differences in fatigue or weakness between the two treatment groups (Ryanodex versus Dantrium).
10. MIP and MEP were highly variable and results were not supported or consistent with results of ABG measurements, indicating that this assessment was not meaningful for the study.

The treatment-emergent adverse events for this trial are summarized in Table 31 below.

Table 31. Treatment-emergent adverse events (Table 12-21, p. 81-82 of the Final Study Report)

System Organ Class [1] Preferred Term [1]	1.0 mg/kg		1.75 mg/kg		2.0 mg/kg		2.25 mg/kg		2.5 mg/kg	
	A (N=3)	B (N=3)	A (N=4)	B (N=4)	A (N=4)	B (N=4)	A (N=4)	B (N=4)	A (N=15)	B (N=16)
Number of Subjects with at least 1 Treatment Emergent Adverse Event	0	2 (67)	2 (50)	3 (75)	2 (50)	2 (50)	2 (50)	3 (75)	11 (73)	9 (56)
Blood and lymphatic system disorders	0	0	0	0	0	0	0	0	0	1 (6)
Neutropenia	0	0	0	0	0	0	0	0	0	1 (6)
Cardiac disorders	0	0	0	0	0	0	0	0	2 (13)	0
Atrioventricular block	0	0	0	0	0	0	0	0	1 (7)	0
Tachycardia	0	0	0	0	0	0	0	0	1 (7)	0
Eye disorders	0	1 (33)	1 (25)	0	0	0	0	0	0	1 (6)
Asthenopia	0	0	0	0	0	0	0	0	0	1 (6)
Vision blurred	0	1 (33)	1 (25)	0	0	0	0	0	0	0
Gastrointestinal disorders	0	0	0	3 (75)	1 (25)	1 (25)	0	1 (25)	5 (33)	3 (19)
Dysphagia	0	0	0	3 (75)	0	0	0	0	3 (20)	1 (6)
Nausea	0	0	0	0	1 (25)	1 (25)	0	1 (25)	2 (13)	1 (6)
Vomiting	0	0	0	0	0	1 (25)	0	0	1 (7)	1 (6)
General disorders and administration site conditions	0	0	0	0	1 (25)	1 (25)	0	0	4 (27)	3 (19)
Asthenia	0	0	0	0	1 (25)	0	0	0	0	0
Fatigue	0	0	0	0	0	1 (25)	0	0	0	0

Clinical Review
 Arthur Simone, MD, PhD
 NDA 205579
 Ryanodex (Dantrolene Sodium)

System Organ Class [1] Preferred Term [1]	1.0 mg/kg		1.75 mg/kg		2.0 mg/kg		2.25 mg/kg		2.5 mg/kg	
	A (N=3)	B (N=3)	A (N=4)	B (N=4)	A (N=4)	B (N=4)	A (N=4)	B (N=4)	A (N=15)	B (N=16)
Feeling abnormal	0	0	0	0	0	0	0	0	3 (20)	3 (19)
Infusion site pain	0	0	0	0	0	0	0	0	1 (7)	0
Infections and infestations	0	0	0	0	0	0	0	0	0	1 (6)
Otitis externa	0	0	0	0	0	0	0	0	0	1 (6)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	1 (25)	0	0	1 (7)	1 (6)
Back pain	0	0	0	0	0	0	0	0	0	1 (6)
Muscular weakness	0	0	0	0	0	1 (25)	0	0	0	0
Musculoskeletal chest pain	0	0	0	0	0	1 (25)	0	0	0	0
Pain in extremity	0	0	0	0	0	0	0	0	1 (7)	1 (6)
Nervous system disorders	0	2 (67)	1 (25)	0	1 (25)	2 (50)	1 (25)	2 (50)	3 (20)	4 (25)
Dizziness	0	0	0	0	1 (25)	0	0	0	0	0
Dysgeusia	0	0	0	0	0	1 (25)	0	0	0	0
Headache	0	0	0	0	0	0	0	0	1 (7)	4 (25)
Hypotonia	0	0	0	0	0	0	0	1 (25)	0	0
Somnolence	0	2 (67)	1 (25)	0	1 (25)	1 (25)	1 (25)	1 (25)	2 (13)	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	0	0	0	0	4 (27)	1 (6)
Dysphonia	0	0	0	0	0	0	0	0	4 (27)	1 (6)
Vascular disorders	0	0	0	0	0	0	1 (25)	0	7 (47)	1 (6)

Clinical Review
 Arthur Simone, MD, PhD
 NDA 205579
 Ryanodex (Dantrolene Sodium)

System Organ Class [1] Preferred Term [1]	1.0 mg/kg		1.75 mg/kg		2.0 mg/kg		2.25 mg/kg		2.5 mg/kg	
	A (N=3)	B (N=3)	A (N=4)	B (N=4)	A (N=4)	B (N=4)	A (N=4)	B (N=4)	A (N=15)	B (N=16)
Flushing	0	0	0	0	0	0	1 (25)	0	7 (47)	1 (6)

[1] From MedDRA Version 14.1

A = Ryanodex

B = Dantrium

Discussion

This trial provides the safety and pharmacokinetic information that were hoped for with its predecessor. As the only completed clinical trial conducted with Ryanodex, it was important that it be appropriately designed for the assessments to be made and that it be executed with minimal numbers of amendments, deviations from the protocol, and losses of participating subjects. There was a single amendment that was instituted prior to the initiation of Part 2 of the trial, which was the only part affected by the amendment. There were a number of deviations from the protocol; most of which were related to the assessments of grip strength after the baseline evaluations were made. This issue is discussed below. The other deviations were minor and not likely to have any meaningful impact on the outcomes of the trial, e.g., PK blood draws performed outside of the protocol defined time window. Importantly, for a study with such a small number of subjects enrolled, all of the subjects who received study drug completed the trial.

The PK data showed that dantrolene exposures, based on $AUC_{0-\infty}$ calculations, were similar for Ryanodex and Dantrium; however, the C_{max} values for Ryanodex exceeded those of Dantrium. These data support the extrapolation of the Agency's finding of efficacy for Dantrium to Ryanodex. They also indicate that there may be greater risk associated with Ryanodex due to its 44% higher C_{max} compared to Dantrium. Aside from the differences in C_{max} for the two products, the PK data indicate the half-lives and exposures to the metabolite 5-hydroxydantrolene were similar.

The safety data collected in this trial help to determine whether the transient increase in dantrolene exposure associated with the higher C_{max} for Ryanodex adversely affects the product's risk profile compared to that of Dantrium. In this regard, it may have been fortuitous that Trial 1201A was not amended multiple times after its initiation and then completed. That could have led to results that were too confounded to be interpreted, but the trial identify problems with some of the assessments, e.g., MIP/MEP and strength assessments, that were key to evaluating safety and permitted the resolution of those problems prior to the start of Trial 1201.

The Applicant was thorough in the clinical laboratory, vital sign, and ECG assessments made, and the timing of those assessments was reasonable for both parts of the study. There were no clinically relevant abnormalities or shifts from baseline that were observed for any of the parameters measured, and there were no clinically relevant differences between Ryanodex and Dantrium for any of those parameters. For the clinical laboratory assessments, these determinations were predicated on the laboratory's ranges of normal values.

The Applicant's assessments of strength and pulmonary function, as it relates to strength, were important given the differences for the two treatments that were observed in the previous trial and the effects of dantrolene as a muscle relaxant. In this trial, hand grip strength declined after dosing in all dose groups. It was more pronounced and occurred more rapidly in the Ryanodex treated subjects at all but the

2.5 mg/kg treatment group for which the decline in hand grip strength both in magnitude and duration was similar between the two treatment groups. There was a concern raised, as noted above, regarding the protocol deviations related to this finding. Changing the assessments of strength from the weaker to the stronger hand after baseline measurements had been made may have made Ryanodex, for which this occurred 9 times, appear less likely to affect strength than it truly did and to diminish its difference compared to Dantrium, for which the switch to the stronger hand occurred only 3 times. While it may not be possible to determine the exact magnitude of the loss of strength or of the difference between the two products, the fact that the loss of strength occurs is sufficient to warrant labeling of the product to make clinicians and patients aware of the risk and to assure that patients are appropriately monitored for signs of weakness and they are not permitted to ambulate unassisted while there is a possibility that their strength is not adequate to support themselves. Given the indications for the use of Ryanodex, and Dantrium, this risk is small compared to the benefit and may not be observed when the products are used to treat an MH episode while the patient is unconscious, intubated, and mechanically ventilated.

The risks from muscle weakness are greater if they affect a patient's ability to adequately ventilate. In this study, the maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) measurements showed significant declines for some subjects; however, there was substantial individual variability for both parameters. The arterial blood gas (ABG) measurements did not indicate any changes that would correspond to inadequate ventilation. The Applicant noted that a single subject in all but the lowest (1.0 mg/kg) dose group had MIP measured below 40 cmH₂O that occurred without changes in ABGs or symptoms indicative of respiratory insufficiency. This threshold was crossed by subjects taking both Ryanodex and Dantrium, and as postulated by the Applicant, may have been related to low baseline measures or variations in subject effort rather than drug effect. Regardless, of the cause, the finding warrants careful monitoring of patients treated with either product. Such monitoring is routinely performed in the operating room and post-anesthesia care units; such monitoring should be required in the holding area for patients receiving either product prophylactically. As with muscle weakness in general, the risk of depressed ventilatory effort appears to be small compared to the benefits of dantrolene and may not be observed when the products are used to treat an MH episode while the patient is unconscious, intubated, and mechanically ventilated.

The Likert Scale findings related to strength correlated with the changes in hand grip strength. The Applicant note that the weakness noted in the scale and seen in hand grip measurements was rarely reported spontaneously to the study staff as an adverse event. They indicated that subjects were assessed for grip strength and MIP/MEP at close to the times they completed the Likert Scale so they may have been aware of changes in strength that they would not notice the rest of the time while they were kept at rest. The results of head lift, calf raises, and stair climb indicated the return of muscle function to an ambulatory state in all subjects after dosing.

The Applicant reported that the other parameters assessed using the Likert Scale (dizziness, fatigue, and nausea) indicated no substantial changes from baseline at any dose in either treatment group. This was true for the groups of subjects; however, for individual subjects who experienced these reactions, the changes occurred within minutes following study drug administration, were generally most intense over the first couple of hours, were mostly rated 1 or 2 out of 5, and were mostly resolved by the 24 hour evaluation.

Lastly, the adverse event profiles for Ryanodex and Dantrium did not show any marked differences for the two products or indicate any clear dose dependency for the adverse events. The number of subjects overall was small, and the trial was not designed to detect significant differences in the occurrence of adverse event. For the limited number of subjects treated, there were no adverse events that were not reasonably expected based on the Dantrium label, and no adverse events for which further investigation would be warranted.

Conclusions

The trial provided a pharmacokinetic basis for extrapolating the Agency's previous finding of efficacy for Dantrium to Ryanodex. It further demonstrated that the pharmacokinetic properties of Ryanodex are similar to Dantrium with the exception of C_{max} for which Ryanodex was observed to have a 44% higher value than Dantrium.

From a safety perspective, the trial indicated that Ryanodex and Dantrium were associated with similar risks for adverse events, and the types of adverse events associated with Ryanodex were similar to those observed in subjects treated with Dantrium and those already described in the Dantrium label.

The 2.5 mg/kg dose of dantrolene that is generally used for the prophylaxis of malignant hyperthermia and administered to conscious patients prior to their anesthetic is generally well tolerated but can be associated with side effects that should be monitored, and if necessary, treated. These include muscle weakness, possible ventilatory depression, nausea, dizziness and fatigue.

The trial demonstrated that the benefits of Ryanodex should be the same as those for Dantrium, and that there is no clinically significant increase in risk with Ryanodex versus Dantrium.

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/s/

ARTHUR F SIMONE
07/02/2014

RIGOBERTO A ROCA
07/02/2014