NCT03189433

Protocol EGL-4104-C-1702:

Phase 2, Multiple-Site, Open-Label, Randomized, 2-Group, Parallel Study to Assess the Efficacy and Safety of Ryanodex® (EGL-4104) as Adjuvant Treatment in Subjects With Psychostimulant Drug-Induced Toxicity (PDIT)

Document Date: September 6, 2017

Clinical Study Protocol

Amendment 1

Protocol Title:	Phase 2, Multiple-Site, Open-Label, Randomized, 2-Group, Parallel Study to Assess the Efficacy and Safety of Ryanodex® (EGL-4104) as Adjuvant Treatment in Subjects With Psychostimulant Drug-Induced Toxicity (PDIT)
Protocol Number:	EGL-4104-C-1702
Date of Protocol:	06 SEPTEMBER 2017
Product:	Ryanodex® (EGL-4104)
IND No.:	[redacted]
Study Phase:	2
Sponsor:	Eagle Pharmaceuticals, Inc. [redacted]
Sponsor's Medical Monitor:	Adrian J Hepner, MD, PhD Phone: +1 (201) 326-5300
Principal Investigator:	[redacted]

Confidentiality Statement

This confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

SIGNATURES

PROTOCOL TITLE: Phase 2, Multiple-Site, Open-Label, Randomized, 2-Group, Parallel Study to Assess the Efficacy and Safety of Ryanodex® (EGL-4104) as Adjuvant Treatment in Subjects With Psychostimulant Drug-Induced Toxicity (PDIT).

PROTOCOL NO: EGL-4104-C-1702 – Amendment 1

Adrian J. Hepner, MD, PhD Executive Vice President & Chief Medical Officer Eagle Pharmaceuticals, Inc.	Date

Protocol EGL-4104-C-1702 – Amendment 1

Summary of Changes

Section	Original Protocol (12 JUNE 2017)	Amendment 1 (06 SEPTEMBER 2017)	Reason for Change
[redacted]	Inclusion Criterion [redacted] [redacted]	Inclusion Criterion [redacted]: Core body temperature obtained rectally of >39.5° C (103.1° F).	[redacted]
[redacted]	Inclusion Criterion [redacted] [redacted]	Inclusion Criterion [redacted] Organ dysfunction, as evidenced by a LODS score ≥ 6. In the event of any delay in obtaining the lab results for baseline LODS score determination, subject may be enrolled [redacted] after enrollment if the pending baseline LODS score turns out to be < 6, subject will be withdrawn from the study and subsequently replaced with a [redacted] for determination.	[redacted]
[redacted]	Inclusion Criterion [redacted] [redacted]	Inclusion Criterion [redacted] Known or suspected recent use of a psychostimulant drug, in the judgement of the Investigator.	[redacted]
[redacted]	Inclusion Criterion [redacted] [redacted]	Inclusion Criterion [redacted] Negative pregnancy test for females. [redacted] In the	[redacted]

Section	Original Protocol (12 JUNE 2017)	Amendment 1 (06 SEPTEMBER 2017)	Reason for Change
	[redacted]	event of any delay in obtaining pregnancy test result, subject may be enrolled and randomized if all the other eligibility criteria are met. [redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

1.0 SYNOPSIS

Name of Sponsor/Company:	Eagle Pharmaceuticals, Inc.
Name of Finished Product:	Ryanodex® (EGL-4104) (dantrolene sodium for injectable suspension)
Name of Active Ingredient:	dantrolene sodium
Title of Study:	Phase 2, Multiple-Site, Open-Label, Randomized, 2-Group Parallel Study to Assess the Efficacy and Safety of Ryanodex® (EGL-4104) as Adjuvant Treatment in Subjects With Psychostimulant Drug-Induced Toxicity (PDIT).
Protocol No:	EGL-4104-C-1702 – Amendment 1
Principal Investigator:	[redacted]
Study sites:	Pre-Hospital Emergency Care (PHEC) units in the United States
Study duration [redacted]	**Phase:** 2

Psychostimulant-Induced Intoxication (PDIT)

PDIT is a life-threatening condition characterized by sudden onset and fast progression. PDIT occurs secondary to illicit use of psychostimulant drugs (e.g., MDMA, methamphetamine, methylone) for recreational purposes, often taken at mass gathering events where performing intense physical activity in high ambient temperature is commonly observed, such as large music festivals and concerts. The main clinical characteristics of PDIT include core body hyperthermia of >39.5° C (103.1° F) and changes in mental status such as agitation, delusions, hallucinations, seizures or even coma. Other signs and symptoms often include tachycardia, tachypnea, rhabdomyolysis, dehydration, acidosis and hyperkalemia. Current treatment includes cooling measures (e.g. ice packs, evaporative cooling, cold water immersion), sedative agents (e.g. benzodiazepines, ketamine) and supportive measures. Treatment delay often leads to serious complications including cardiac arrhythmias, coagulation disorders and organ dysfunction, which may result in long-term sequelae or even death.

Mass-Gathering Medicine

Hundreds of mass gatherings, including city marathons, parades, concerts, and music festivals, occur throughout the US each year and, in general, they are safe and enjoyable events. However, attendees at these events can be isolated from access to regular emergency services and medical care, and illness, injuries, and fatalities do occur.

Mass gatherings require health and medical services, harm-reduction strategies, operational plans, and emergency contingency plans to be in place. A mass gathering can be defined as any occasion that attracts

sufficient people to strain the planning and resources of the community, city, or nation hosting the event. Mass-gathering medicine (MGM) is a young and rapidly evolving discipline with ties to emergency medicine, disaster medicine, and public health.

Mass gatherings take place in dynamic environments. Planning and provision of health and emergency medical services is challenging. Patterns of injury and illness differ from those typically encountered in the community. Medical responses are complicated by logistical challenges, such as weather extremes, crowding, site access, geographical barriers and communication difficulties. These unique challenges, along with increased rates of morbidity, mean that baseline 911 emergency services alone are not enough to ensure the safety of attendees. As well, there is a growing awareness of the impact of mass gatherings on local communities and a requirement to avoid compromising baseline emergency services. Consequently, there is a shift away from a standard first-aid model of care and toward on-site multidisciplinary medical teams (e.g., physicians, nurses, paramedics) offering a higher and more complex level of care, which includes similar capabilities as those commonly available at an emergency department of a regular community hospital.

Objectives

Primary: To evaluate the efficacy of Ryanodex® for the treatment of PDIT, administered as an adjuvant treatment to the current standard of care (SOC).

Secondary: To evaluate the safety and tolerability of Ryanodex® for the treatment of PDIT administered as an adjuvant treatment to current SOC.

Methodology

Study EGL-4104-C-1702 is a phase 2, multiple-site, open-label, randomized, 2-group parallel study of Ryanodex® for the treatment of PDIT, administered intravenously (IV) as adjuvant treatment to the current SOC, which is defined as body cooling and supportive measures, including treating related symptoms and any existing comorbidities. Due to the acute and serious nature of PDIT, more commonly occurring in young individuals attending mass gathering events (e.g. large music festivals and concerts), and the importance of early diagnosis and fast implementation of treatment, the study will be conducted at qualified pre-hospital emergency care facilities [PHEC]. The PHECs are medical units fully equipped and staffed to provide adequate emergency medical care to patients with PDIT. This study is designed to evaluate the safety and efficacy of Ryanodex® in this acutely ill patient population in an emergency setting, where study subjects are anticipated to be treated over a short period of time and then transferred to another medical facility or released, depending on their overall medical status. In order to standardize subject's evaluation, data collection and subsequent analysis, functioning of each organ system will be assessed individually and will also be conducted using the Logistic Organ Dysfunction System (LODS).

After diagnosis of PDIT, the Investigator should initiate SOC treatment as quickly as possible, and will assess the subject's eligibility for study participation. The Investigator will document subject's baseline status.

Body cooling measures should be stopped at the first instance of rectal temperature [redacted] hypothermia.

Enrolled study subjects are expected to remain at the study site for a maximum of 6 hours after screening, prior to discharge from the study site. Subjects who require hospitalization beyond [redacted] after Screening (e.g., because of complications, adverse events [AEs], or other reasons) will complete the required study discharge procedures prior to their continuation of care outside of the study. The Investigator will make all reasonable efforts to obtain subjects' medical data from these medical facilities.

Logistic Organ Dysfunction System

The Logistic Organ Dysfunction System (LODS) provides an objective tool for assessing organ dysfunction in critical patients. The LODS identifies organ dysfunction for 6 organ systems: neurologic, cardiovascular, renal, pulmonary, hematologic and hepatic, taking into account both the relative severity among organ systems and the level of severity within an organ system.

Standard of Care

Implementation of standard of care (SOC) should be initiated as quickly as possible after admission of the subject to the PHEC. For the purpose of this study, SOC is defined as efficient body cooling by physical methods and supportive measures, implemented as following:

Body Cooling

- ***Ice packs****: should be placed to neck, axilla, and inguinal regions.*
- ***Evaporative cooling****: application of water (room temperature) over the body surface, via mist application with continuous use of a fan. Subjects may be covered with a thin sheet. Do not use ice/cold water immersion because of concerns with shivering (which could potentially worsen hyperthermia), and the need for IV access and other monitoring measures and medical procedures.*
- ***Benzodiazepines****: may be administered to ameliorate shivering induced by cooling methods, as deemed necessary by the Investigator.*

Supportive Measures

Randomized subjects will also receive any other medical treatments and/or supportive measures (IV fluids, respiratory support) for the adequate treatment of existing complications or comorbidities (e.g. dehydration, seizures, aggressiveness, asthma) following acceptable medical practice, and as deemed necessary by the Investigator.

Treatment Groups

Upon admission to the PHEC, eligible patients with PDIT will be randomized in a [redacted] ratio to one of the following treatment groups:

- Group A: Ryanodex®, as added treatment to SOC
- Group B: SOC only

The Investigator will make all reasonable efforts to perform the [redacted] drug screen test during the screening process or as soon as feasible after randomization. The [redacted] drug screen test may not be feasible in some subjects, due to the dehydration, use of oxygen therapy and/or endotracheal intubation commonly seen in patients with PDIT, which may result in dryness of the oral mucosa. A blood sample for testing for the presence of psychostimulant drugs will also be collected after randomization.

Subjects in Group A will receive SOC immediately followed by an initial dose of Ryanodex® (study drug) of 2.5 mg/kg administered as an IV bolus. Initial dose of Ryanodex® should be administered within [redacted] minutes of randomization. The goal is to achieve an adequate clinical response, which is defined as meeting both of the following criteria:

[redacted]

2. Logistic Organ Dysfunction System (LODS) score ≤ 5

If the subject is not showing adequate clinical response between 10 and 30 minutes after the initial dose, or the subject had achieved an adequate response but afterwards signs/symptoms believed to be associated with PDIT re-appear [redacted] a second IV bolus dose of 2.5 mg/kg of Ryanodex® may be administered between 10 and 30 minutes following the initial dose. This repeat dosing is permitted, as deemed necessary by the Investigator, unless the subject demonstrates clinically significant signs/symptoms of dantrolene-related adverse reactions.

The Investigator must clearly record all clinical assessments and symptoms leading to repeat dosing of Ryanodex®. The total administered dose of Ryanodex® in a 24-hour period should not exceed 10 mg/kg.

Individual Subject Stopping Rules

- The Investigator may consider stopping study drug if the subject demonstrates clinically significant signs/symptoms of dantrolene toxicity, which may include, but are not limited to, the following: increased skeletal muscle weakness; worsening in the state of consciousness (e.g., lethargy, coma); worsening respiratory status, including increased respiratory muscle weakness, vomiting, diarrhea, or crystalluria; providing none of these signs/symptoms are not attributable to PDIT, a comorbid condition (e.g., asthma, epilepsy, pneumonia) or a concomitant medication (e.g., sedatives).
- The Investigator may stop study drug at any time for that subject's well-being if the Investigator believes that the subject has experienced a serious AE (SAE) possibly related to study drug or a clinically significant non-serious AE possibly related to study drug.
- The subject will be withdrawn from the study if a diagnosis had been made for which dantrolene is the SOC (e.g., malignant hyperthermia [MH]), and treatment with commercially available dantrolene should be initiated.
- In case a subject was unable to provide consent at the time of enrollment due to the severity of their condition (in accordance with the provisions in 21 CFR 50.24), once the subject is able to understand the nature of the study and the consenting process or the subject's relative becomes available, the subject or relative will be informed that the subject has been enrolled in a clinical study and has been treated on an emergency basis with either standard of care (SOC) or with SOC plus an investigational drug. If the subject or relative refuses consent, the Investigator will stop study assessments and procedures at that time, withdraw the subject from the study, and will not perform any subsequent study assessments.

Study Phases

The study will include the following phases: Screening/Baseline, Treatment Phase, and Discharge.

Planned number of subjects:	An estimated total of 100 subjects will be enrolled in the study (approximately 50 per group). [redacted] Safety evaluations will be analyzed for all randomized subjects who have received study treatment.
Diagnosis and main criteria for inclusion:	Male or non-pregnant female subjects, aged 18 years or older, will be eligible for entry into this study if they are diagnosed with PDIT, as evidenced by all the following at Screening: • Core body temperature obtained rectally of >39.5° C (103.1° F). • LODS score ≥ 6. In the event of any delay in obtaining the lab results for baseline LODS score determination, subject may be enrolled and randomized if all the other eligibility criteria are met; after enrollment if the pending baseline LODS score turns out to be < 6, subject will be withdrawn from the study and

	subsequently replaced with a new subject to complete the ITT population. • Known or suspected recent use of a psychostimulant drug, in the judgement of the investigator. • Negative pregnancy test for female subjects. If positive, female subjects must be excluded from participating in the study. In the event of any delay in obtaining pregnancy result, subject may be enrolled and randomized if all other eligibility criteria are met. However, female subjects randomized to Treatment Group A (Ryanodex as adjuvant treatment to SOC) must not be dosed with Ryanodex until a negative result of the pregnancy test is available. If a positive pregnancy test is noted after randomization, subject will be withdrawn from the study and subsequently replaced with a new subject to complete the ITT population.
Main criteria for exclusion:	A subject diagnosed with PDIT will be excluded from entering the study if he or she presents with or, in the judgment of the Investigator, meets any of the following criteria at Screening: • Diagnosed with or is suspected to have an acute clinically severe infection, which in the opinion of the Investigator may increase the subject's risk for participating in the study and/or may impair the ability of performing and/or interpreting study assessments. • Severe hyperthermia secondary to a condition other than PDIT (e.g., thyrotoxicosis, pheochromocytoma, or brain hemorrhage). • Likelihood of head trauma in the past 3 months, or other systemic disease that might increase the subject's risk for participating in the study and/or may impair the ability of performing and/or interpreting study assessments. • Positive pregnancy test or evidence of active lactation. • Known history of allergy or hypersensitivity to dantrolene. • Known history of seizure disorders or epilepsy.

	• Current or prior use (within the past 2 weeks) of calcium channel blockers.
Test product, dose, and mode of administration:	**Ryanodex®:** dantrolene sodium for injectable suspension; 250 mg/vial to be reconstituted in 5 mL of sterile water for injection (without a bacteriostatic agent) to yield a 50 mg/mL suspension; to be administered as a rapid IV push of 2.5 mg/kg.
Reference therapy, dose, and mode of administration:	**Standard of Care (SOC):** all subjects in both treatment groups will receive SOC. **Supportive Measures:** all subjects should receive adequate supportive measures for treating PDIT, as well as medically acceptable treatment for complications and comorbidities.

Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint for this study is proportion of subjects achieved a total LODS score ≤ 5 at or prior to 60 minutes post-randomization.

Secondary Efficacy Endpoints:

- Proportion of subjects who achieved a LODS total score ≤ 5 at planned time points.

[redacted]

Dantrolene plasma concentration:

Plasma sample data will be presented for all subjects with informed consent and/or summarized.

Safety Assessments:

- Adverse events (AEs)
- Vital signs (blood pressure, respiratory rate, and pulse)
- Clinical safety laboratory tests (hematology and coagulation parameters, and blood chemistry)
- Electrocardiogram (ECG)

- Physical examination
- Brief neurological examination
- Oxygen saturation (measured with pulse oximeter)
- End-tidal CO_2 ($ETCO_2$)

Sample size:
A planned sample size of 100 (50 per treatment group) fully eligible (for efficacy) subjects are planned to be randomized in this study. [redacted]

Baseline:

Baseline body temperature will be the first rectal temperature >39.5° C (103.1° F) taken during the Screening Phase. Baseline results for other study assessments will be the value closest in time to the baseline rectal temperature and prior to randomization. The SAP may specify additional data handling rules.

Analysis populations:

The Intent-to-Treat (ITT) population is defined as all randomized subjects whose screening test results for presence of a psychostimulant drug was confirmed by blood test. The ITT population will be used as the primary efficacy population.

The Modified Intent-to-Treat (MITT) population is a subset of the ITT population excluding the subjects who are intubated or with mechanical ventilation or CPAP.

The Per Protocol population (PP) is defined as all ITT subjects who met all inclusion/exclusion criteria, have a baseline and at least 1 post-baseline LODS score, and have no major protocol deviations that could affect the efficacy assessments.

The Safety population is defined as all randomized subjects who received any study treatment (SOC only or SOC with Ryanodex®). The Safety population will be used to analyze all safety endpoints using actual treatment received.

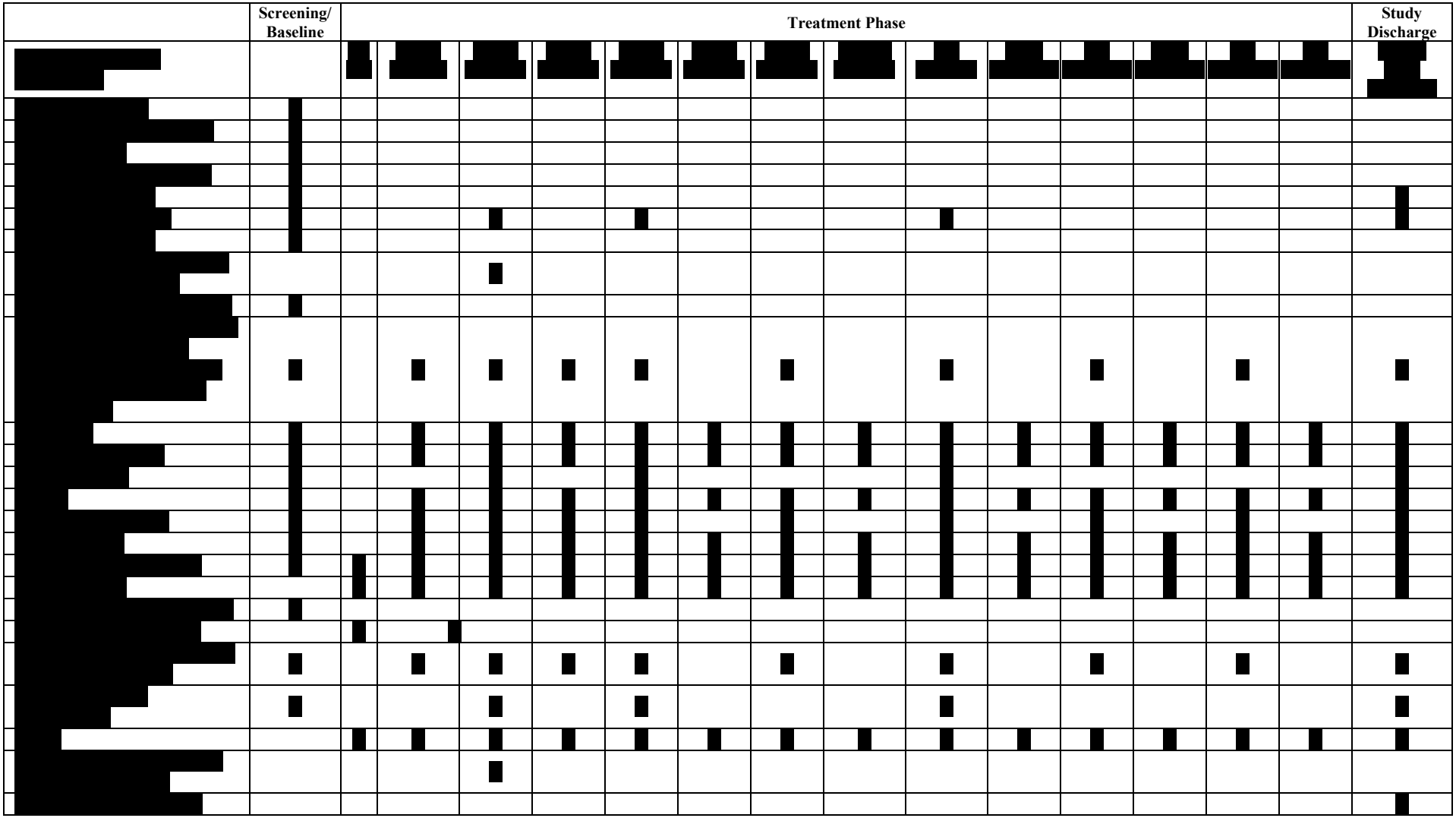
Efficacy Analysis: The primary analyses of the primary and secondary efficacy endpoints will be conducted on the ITT population. The MITT and PP population analyses of primary and secondary endpoints will be considered supportive.

[redacted]

Safety Analysis:

Safety Population will be used for the safety analysis. No modeling or inferential statistics will be conducted on the safety assessments.

Table 1: Schedule of Assessments



Abbreviations: CCM = continuous cardiac monitoring; $ETCO_2$ = end-tidal carbon dioxide; ECG = electrocardiogram; med = medication; min = minutes; PT = prothrombin time