

1. CLINICAL TRIAL PROTOCOL

**PILOT PHASE 1/2, OPEN-LABEL, CLINICAL TRIAL TO
InVESTIGATE CT38 iN THE TREATMENT OF MYALGIC
ENCEPHALOMYELITIS / CHRONIC FATIGUE
SYNDROME (InTiME)**

Protocol Title: InTiME
Protocol Number: ME-101p
Protocol Date: May 25, 2018, Amended July 3, 2018 (version 1.2); Amended October 26, 2018 (version 1.51), Amended December 7, 2018 (version 1.62)
Development Phase: 1/2
Drug Substance: CT38
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clinicaltrials.gov: NCT03613129

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Title: InTiME

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Reviewed and Approved by:

Lucinda Bateman, MD, Principal Investigator

Hunter Gillies, MD, Medical Monitor

LISTING OF ABBREVIATIONS AND DEFINITION OF TERMS

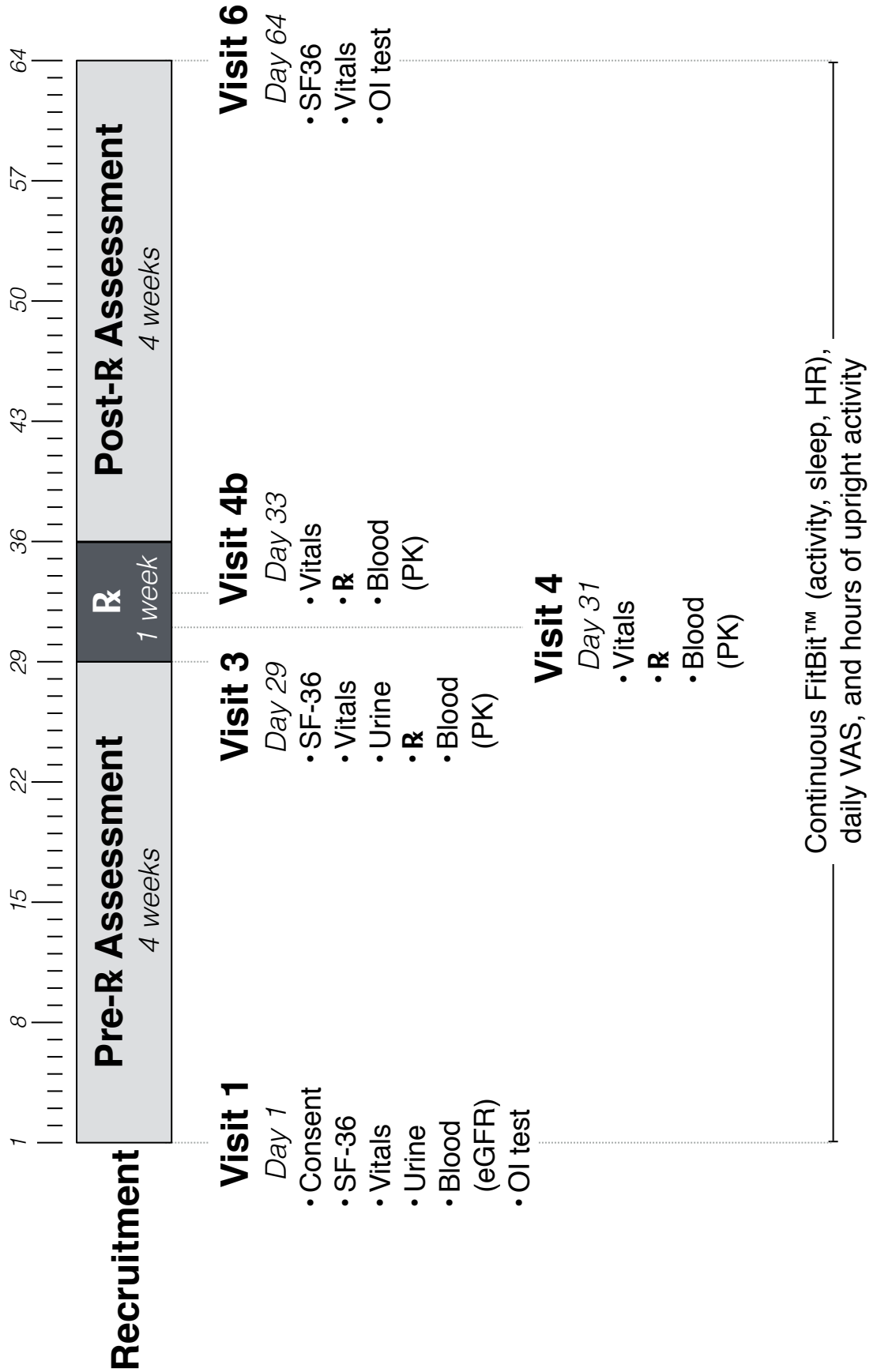
5HT: Serotonin	IND: Investigational New Drug
5HT _{1A} : Serotonin receptor subtype	IRAE: Immediately reportable adverse event
AE: Adverse event	IRB: Institutional Review Board
AUC: Area under the plasma concentration-time curve from time zero to infinity	ME: Myalgic Encephalomyelitis
BNST: Bed nucleus of the stria terminalis	MTD _b : Maximum tolerated dose by bolus
BP: Blood pressure	OI: Orthostatic intolerance
BPM: Beats per minute	PEM: Post-exertional malaise
CFS: Chronic Fatigue Syndrome	PI: Principal Investigator
C _{max} : Maximum plasma concentration	PD: Pharmacodynamic
CPET: Cardio-pulmonary exercise test	PK: Pharmacokinetic
CRF: Corticotropin-releasing factor	RAND36: Medical Outcomes Survey (similar to Short Form-36)
CRF ₁ , CRF ₂ : Corticotropin-releasing factor receptor, subtype(s) 1 and 2	RER: Respiratory exchange ratio
C _{ss} : Plasma concentration at steady state	RPE: Rating of perceived exertion
CT37: Originally PG-873637	SAE: Serious adverse event
CT38: Originally PG-873638 (free base)	SC: Subcutaneous
CT38s: Originally PG-968041, acetate salt of CT38	SNRI: 5HT and norepinephrine re-uptake inhibitor
EEG: Electroencephalography	SSRI: Selective 5HT re-uptake inhibitor
eGFR: Estimated glomerular filtration rate	t _{1/2,z} : Terminal elimination half-life
FDA: Food and Drug Administration	VAS: Visual analogue scales
HPA: Hypothalamic-pituitary-adrenal	VCO ₂ : Carbon dioxide production
HR: Heart rate	Ve: Minute ventilation
IB: Investigator's Brochure	VO ₂ : Oxygen consumption
ICH: International Conference on Harmonization	V _T : Ventilatory threshold
	UCN2, UCN3: Urocortins 2 and 3

PROTOCOL SYNOPSIS

Title	InTiME: Pilot Phase 1/2, Open-Label, Clinical Trial to <u>I</u> nvestigate <u>CT38</u> in the Treatment of <u>M</u> yalgic <u>E</u> ncephalomyelitis / Chronic Fatigue Syndrome
Indication	Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
Protocol Number	ME-101p
Study Sponsor	Lucinda Bateman, MD Bateman Horne Center
Principal Investigator	Lucinda Bateman, MD Bateman Horne Center
Study Sites	The study will be conducted at a single center in the US.
Clinical Phase	1/2
Study Period	Planned duration of the study (for each patient): 9 weeks Planned recruitment period: 12 weeks
Objectives	To evaluate the efficacy of CT38 in the treatment of ME/CFS, based on changes in patient-reported symptoms (e.g., fatigue, pain, sleep, cognition, orthostatic intolerance, temperature, flu-like, headaches or sensitivities, shortness of breath, gastrointestinal, urination, anxiety, depression), hours of upright activity, functional capacity (activity, sleep quality, energy expenditure, heart rate), and general health status (global change, vitals) To evaluate the effect of CT38 on orthostatic intolerance To gain preliminary insights on the safety and tolerability of CT38 in ME/CFS patients
Study Design	Single-center, open-label, 3-arm Phase 1/2 clinical trial The study is comprised of a screening and recruitment period, a 4-week pre-treatment assessment period, a 1-week interventional treatment period, and a 4-week post-treatment assessment period
Duration of Treatment	3.5 hours at each of Visits 3, 4 and 4b (total of 10.5 hours)
Number of Patients	Total of 18, with at least 3 in each of D1 and D2 dose groups (sequentially-dosed) and the remainder allocated to a final dose determined by D1/D2 tolerability
Study Agent	CT38s, a peptide agonist selective for the corticotropin-releasing factor receptor subtype 2, delivered by subcutaneous administration

Dosing	<p>The study will utilize a continuous subcutaneous infusion at 3 dose levels. The planned Low-dose delivered ~0.8 µg/kg over 3.5 hours (on 2 separate treatment days), was associated with clinically significant hemodynamic changes, and is closed out.</p> <p>The revised doses will deliver 0.11 and 0.35 µg/kg by continuous subcutaneous infusion.</p>
Inclusion Criteria	<p>Able to read, understand and voluntarily sign the informed consent form</p> <p>18-60YO male or female, meeting Fukuda, Canadian and IOM criteria for ME/CFS, and relatively stable state of illness for the past 3 months</p> <p>Agree to refrain from taking medications that would affect assessment of the effectiveness of study medication for the duration of the study</p> <p>Living at an altitude between 3,500 and 5,500 feet above sea level for the past 1 year</p> <p>Availability for the duration of the study</p> <p>Have mobile (smart) phone and access to the internet</p>
Exclusion Criteria	<p>Alternate medical or psychiatric illness that explains ME/CFS symptoms</p> <p>Active or uncontrolled co-morbidities (including depression, untreated endocrine diagnoses, recent acute infection, the presence of a supra-ventricular tachycardia or ventricular tachycardia, severe baseline hypotension, etc), which in the opinion of the PI may interfere with the ability of the patient to participate in the study</p> <p>Pregnancy, or while breast feeding</p> <p>Cigarette smoker or former smoker who has smoked within 6 months of the study</p> <p>Renal impairment, Body Mass Index > 35, or evidence of substance abuse</p> <p>Participating in another clinical treatment trial, or symptoms improving as a result of treatment intervention in the past 3 months</p> <p>Current treatment with medications that interact with the 5HT, norepinephrine, dopamine or cortisol pathways</p> <p>Treatment with short-term antivirals/antibiotics within 4 weeks, Rituximab™ within 6 months, or anti-retrovirals within 1 year, of entry into the trial.</p>
Efficacy Evaluation	<p>Primary Endpoint: The change in patient-reported daily symptom levels</p> <p>Secondary Endpoints, include a determination of treatment-related effects on functional capacity, orthostatic intolerance and general health status</p>
Safety Evaluation	<p>Adverse events occurring after patient enrollment through to the final visit to the clinic, will be assessed and recorded. Serious adverse events deemed related to study treatment will be followed until resolution or stabilization of the event.</p>

SCHEMATIC OF STUDY DESIGN



1.1. Introduction

1.1.1. Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), also known as systemic exertion intolerance disease, is a complex disorder that may be triggered by infection or other stressors (e.g., emotional or physical trauma, immune activation, chemical exposures). Its hallmark is a reduced capacity for physical and mental activity manifest as profound fatigue along with a cascade of debilitating symptoms (including pain, cognitive dysfunction, orthostatic intolerance, sensitivities, and irregularities of the autonomic, immune and metabolic systems) that worsen with activity (referred to as post-exertional malaise or PEM), are not improved by sleep, and can persist for years. ME/CFS affects up to 2.5 million Americans and results in annual direct and indirect economic costs between \$17 and 24 billion in the US. There are no approved therapeutics for ME/CFS. Patients are often unable to handle the activities of daily living and experience a loss of career and a very poor quality of life [IOM 2015].

The etiology of ME/CFS is unknown. The disease is often thought of as a stress- and/or neuroendocrine-related complication, with patients showing abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis and of the immune, metabolic, norepinephrine and serotonin (5HT) systems. In young animals, intense stress can bring about an up-regulation and relocation of the corticotropin-releasing factor receptor subtype 2 (CRF₂) to the membranes of 5HT neurons in the raphe nuclei (i.e., the source of 5HT in the brain and cord) and limbic system, which can persist into adulthood. In this configuration, a minor stress stimulates (rather than inhibits) the release of 5HT from the raphe nuclei and throughout the limbic system, and the excess of 5HT leads to a desensitization of the 5HT_{1A} autoreceptor and compromised 5HT regulation [Wood 2013, Neufeld-Cohen 2012, Lukkes 2009a, Lukkes 2009b, Waselus 2009, Lukkes 2008]. Cortene Inc. (see below) has postulated that ME/CFS results from such CRF₂ up-regulation and relocation, and relative to healthy subjects, ME/CFS patients show increased brain and/or hypothalamic 5HT [Dinan 1997, Sharpe 1997, Bearn 1995, Cleare 1995, Bakheit 1992], 5HT_{1A} desensitization [Cleare 2005] and higher positivity for 5HT serum antibodies that correlate with increased physio-somatic symptom scores (muscle pain, autonomic symptoms, flu-like malaise) and sadness [Maes 2013]. This hypothesis of a CRF₂ maladaptation, resulting in an excess of 5HT under subsequent stress, comprehensively explains the symptoms and anomalies of ME/CFS. However, in the absence of an animal model of ME/CFS, the hypothesis can only be investigated in humans.

1.1.2. Investigational Agent

CT38 [proprietary data redacted] is a custom [proprietary data redacted] CRF₂-selective, peptide agonist...[proprietary data redacted] comprised of naturally-occurring amino acids, and is easily synthesized [Investigator's Brochure or IB].

CT38 was previously filed under investigational new drug (IND) application [proprietary data redacted], with the Division of Metabolism and Endocrine Drug Products at the Food and Drug Administration (FDA), to evaluate its effect in preventing muscle atrophy and wasting associated with various disease conditions. Completed studies included all the pre-IND studies (necessary for an acute indication) as well as a Phase 1 clinical trial in healthy humans. Full study reports were submitted to the FDA under IND [proprietary data redacted], and there were no outstanding issues when the IND was voluntarily withdrawn in 2008 (for strategic reasons unrelated to CT38). Cortene Inc. ("Cortene") licensed CT38 along with the right of reference to IND [proprietary data redacted].

1.1.2.1. In Vitro Pharmacology

CT38, CT38s (acetate salt of CT38, [proprietary data redacted]), CT37 (backup lead, [proprietary data redacted]), UCN2 and urocortin 3 (UCN3, endogenous CRF₂-selective peptide) were evaluated for selectivity and potency against CRF₁ (via A7r5 rat aortic cell lines) and CRF₂ (via Y-79 human retinoblastoma cell lines), by measuring cyclic adenosine monophosphate (cAMP) formation after treatment with the compound of interest. CT38 was found to have a greater than 50-fold selectivity for CRF₂ over CRF₁, and comparable CRF₂ potency to UCN2 [IB].

1.1.2.2. *In Vivo Pharmacology*

In vivo, CT38, CT37 and other custom CRF₂ agonists show similar beneficial effects to UCN2 and/or UCN3, in animal models of muscle wasting (due to casting, denervation, corticosteroid excess, dystrophin-deficiency), tumor growth and metastases, inflammation, obesity, GI transit time and the cardiovascular system, specifically changes in heart rate (HR) and blood pressure (BP) [IB].

1.1.2.3. *Safety Pharmacology and Toxicology*

There is little or no binding of CT38 when tested against various receptors, transporters, ion channels and enzymes, other than CRF₁ (weakly binding at very high concentrations). CT38 does not cause QT prolongation *in vitro* (in human ether-a-go-go related gene or hERG channel and Purkinje fiber assays) and *in vivo* (rats and monkeys). *In vivo* safety pharmacology studies demonstrate that high doses of CT38, administered as CT38s by the subcutaneous (SC) route, has pharmacological effects on the central nervous system (drop in spontaneous motor activity, decreased body temperature, tremors and subdued behavior), respiratory system (decreased respiratory rate and tidal volume), cardiovascular system (tachycardia, hypotension), gastrointestinal system (decreased transit time), and renal system (enuresis and diuresis) [IB].

Toxicology studies (mouse, rat, dog, rabbit, monkey, human *in vitro*) show that CT38 (administered as CT38s by the SC route) has large safety margins with mostly mild, dose-dependent, transient and reversible effects. CT38 is not genotoxic (*in vitro* Ames and chromosome aberration assays), has no effect on corticosterone and aldosterone levels, and in 1-month repeat dose toxicology studies in rats and monkeys, there was little or no drug accumulation and no antibody formation (histology). CT38 is eliminated by renal filtration and the terminal elimination half-life ($t_{1/2,z}$) is < 2 hours [IB].

In animals, CT38 administered by SC injection (bolus) causes transient, but dose-related increases in HR and decreases in BP, similar to UCN2 and UCN3. These were shown to be much reduced under SC infusion, potentially explained by a lower maximum plasma concentration (C_{max}). However, under continuous SC infusion in rats, the complete absence of tachycardia or hypotension even at dose levels 10,000 times higher than the bolus doses that cause such HR and BP changes, suggests that continuous SC infusion induces receptor (CRF₂) endocytosis. This is consistent with studies showing that the endocytosis of CRF₂ is a function of agonist potency, concentration and duration of exposure [IB].

1.1.2.4. *Phase 1 Clinical Trial*

CT38s was administered by SC injection (bolus) in a sequential, single ascending dose, randomized, double-blind, placebo-controlled trial in healthy male subjects. There were no deaths or serious adverse events (SAEs). Adverse events (AEs) were generally mild and anticipated from CRF₂ pharmacology. Escalating dose (in $\mu\text{g}/\text{kg}$) first caused HR increases at 0.200; tachycardia (> 100 beats per minute or BPM at rest) at 0.833; and hypotension at 1.67. The only AE classified as severe was a single subject with tachycardia (160 BPM) at a dose of 1.667 $\mu\text{g}/\text{kg}$ (resolved with propranolol). The maximum tolerated dose by bolus (MTD_b) was deemed to be 0.833 $\mu\text{g}/\text{kg}$, which showed mild tachycardia without hypotension. The $t_{1/2,z}$ was 1-3 hours. CT38 was not detectable in the plasma 8 hours post-dose. All laboratory results (including cortisol levels and QTc changes) were comparable to placebo, except for white blood cell counts, which were slightly elevated in the highest dose groups, but had resolved by the following day. The clinical study report was submitted to FDA and there were no outstanding concerns when the IND was voluntarily withdrawn [IB].

1.1.2.5. *CT38 in ME/CFS*

If ME/CFS results from an up-regulation/relocation of CRF₂ and a maladapted stress response as postulated above, then prolonged receptor stimulation via a CRF₂ agonist such as CT38, could potentially induce CRF₂ endocytosis (as demonstrated by SC infusion in rats), which could be curative. In addition, CT38 and other CRF₂ agonists can modulate many of the individual abnormalities of the disease (e.g., the HPA axis, the immune system, cortisol, glucose).

There is no animal model of ME/CFS. Moreover, specific changes in CRF₂ expression on specific neurons of the raphe nuclei and limbic system, along with any resulting excess of 5HT in these neurons under

stress, cannot be measured in a live system—though such changes have been demonstrated in animal biopsies. Therefore, assuming the hypothesized etiology is correct, the only possible way to investigate effect in humans is via a clinical trial. Given that CT38 has shown virtually identical pharmacology to the endogenous CRF₂ agonists UCN2 and UCN3, both *in vitro* and *in vivo*, and has been shown to be safe and tolerable in a Phase 1 trial in healthy human subjects, the Principal Investigator (PI), Lucinda Bateman, MD, a clinician with expertise in the diagnosis, treatment and study of ME/CFS, plans to evaluate CT38 as a candidate therapeutic for the treatment of ME/CFS.

1.1.2.6. Initial Experience in ME/CFS Patients

The first 2 patients dosed under this protocol exhibited hemodynamic changes as the infusion progressed (i.e., dose-related). These changes included increased HR (baselines of 47 and 92 BPM, increasing to respective maximums of 89 and 111 BPM, towards the end of the infusion) and decreased BP (baselines of 105/68 and 108/74 mmHg, decreasing to respective minimums of 110/56 and 100/50 mmHg). The associated pharmacokinetic (PK) data... [proprietary data redacted]. This increased sensitivity of the CRF₂ pathway supports the notion that CRF₂ may be up-regulated in ME/CFS patients relative to healthy subjects.

Referring to the IB (section 4.1.1.4.), a concentration of between... [proprietary data redacted]. The hemodynamic effects induced in the first 2 patients dosed under this protocol suggests that the initial dose... [proprietary data redacted] was too high.

The next 3 patients, receiving the revised D1 dose under this amended protocol, showed asymptomatic changes in HR (individual increases of 13-19, 13-22 and 9-28 BPM over baselines) and BP (individual systolic decreases: 12-13, 8-17 and 5-17 mmHg from baseline; individual diastolic decreases: 8-11, 14 and 8-18 mmHg from baseline). ... [proprietary data redacted]. Patient-reported symptom assessments (scale 0-65, see 6.3.1.3.) showed statistically significant improvements in both symptom level and symptom volatility (individual pre-treatment means and standard deviations of 23.57±3.42, 43.91±3.48, 12.87±4.22 decreasing to 15.97±2.21 37.00±3.28 8.11±4.17 post-treatment). These changes are consistent with the postulate that up-regulated CRF₂ in the limbic system increases the sensitivity to stressors and the release of 5HT (and other neurotransmitters) under stress, and thus down-regulating CRF₂ will reduce symptom levels and volatility. ... [proprietary data redacted]. It would thus be beneficial to understand the duration of infusion, in particular whether an additional 3.5-hour infusion will reduce symptom levels and volatility further (as previously contemplated in this protocol, section 6.3.1.5.3.).

To date, patients have been assessed by a variety of exploratory metrics including cardio-pulmonary exercise test (CPET) and cognitive scoring (via DANA mobile software). CPET in particular was intended to be the primary endpoint in this trial. However, the pre-treatment CPETs for all 5 patients do not indicate major patient deficits relative to historical data for healthy subjects, and they do not exacerbate patient symptoms beyond normal day-to-day stressors. Post-treatment CPETs for the 3 patients tested at the D1 dose show slight improvement in CPET parameters and reduced symptom exacerbation relative to pre-treatment exacerbation, but given the constraints that CPET imposes on the overall protocol (altitude, logistics, duration), such testing is not warranted for this essentially proof-of-concept trial. Similarly, due to the lack of sensitivity to DANA cognitive testing, and the burden on subjects to complete these daily assessments, this test will no longer be performed.

Thus, the purpose of this amendment is to add an additional 3.5-hour infusion at the D1 dose, eliminate CPET testing (and associated visits to the clinic) and DANA testing, and to designate patient-reported symptom scores as the primary endpoint.

1.2. Study Objectives

This study seeks to investigate the safety, tolerability and efficacy of CT38 in the treatment of ME/CFS patients, based on the effect of CT38 on symptom levels (e.g., fatigue, pain, sleep, cognition, orthostatic intolerance, temperature, flu-like, headaches or sensitivities, shortness of breath, gastrointestinal, urination, anxiety, depression), functional capacity (activity, sleep quality, energy expenditure, HR and

hours of upright activity), and general health status (global change, HR, BP, oral temperature, respiratory rate), pre- and post-treatment.

1.2.1. **Potential Risks**

The principal risks associated with CT38 are a potential increase in HR and decrease in BP. In the remainder of this trial, CT38 will be dosed via continuous SC infusion, repeated on 3 separate days. The original protocol lowest dose-level was associated with increased HR and decreased BP. The revised dosing utilizes lower rates of infusion and lower total doses. To mitigate risks further, dosing will be sequential, commencing with the lowest dose group and escalating only in the absence of clinically important hemodynamic changes at the preceding dose-level. HR and BP will be monitored during dosing and will have to remain within an acceptable range (see below), as a prerequisite for ascending to the next dose-level.

Beyond the investigational agent itself, there are minor risks associated with needle insertion, for blood sampling or drug administration.

1.2.2. **Potential Benefits**

If the hypothesized up-regulation of CRF₂ is correct, and if the proposed treatment achieves CRF₂ endocytosis (as it likely does in rats—based upon the loss of the ability to induce effects mediated by CRF₂ stimulation), the proposed treatment could reset the receptor within the raphe nuclei and limbic system to pre-ME/CFS levels. This should reduce the sensitivity of the stress response, thereby reducing stress-induced symptom exacerbation. If the receptor remains internalized, the treatment could be curative.

1.3. **Investigational Plan**

1.3.1. **Study Design**

1.3.1.1. *Overview*

This study is a single-center, open-label, 18-patient, 3-arm Phase 1/2 clinical trial, to evaluate safety, tolerability and efficacy of CT38, administered as the acetate salt CT38s, by the SC route of administration, at up to 3 separate dose-levels, for the treatment of ME/CFS.

The study is comprised of a recruitment and screening period, enrollment (Day 1), a 4-week pre-treatment assessment period (Days 1-28), a 1-week interventional treatment period (Days 29-35) with drug infused on Days 29, 31 and 33, a 4-week post-treatment assessment period (Days 36-63), and a close-out (Day 64).

1.3.1.2. *Primary Endpoint*

The primary endpoint will be determined from a pre- and post treatment assessment of visual analog scale (VAS) scores recorded daily for each of 13 symptoms, namely: (i) fatigue; (ii) muscle/joint pain; (iii) sleep problems, e.g., un-refreshing sleep, difficulty falling or staying asleep, excessive sleepiness; (iv) cognitive problems, e.g., slow information processing, memory difficulties, inability to concentrate/focus, attention deficit; (v) orthostatic intolerance; (vi) body temperature perceptions; (vii) flu-like symptoms, e.g., sore throat, tender lymph nodes, swollen glands, fever, chills, sinus/nasal problems; (viii) headaches or sensitivities to light, sound, smell, touch, taste; (ix) shortness of breath; (x) gastrointestinal problems, e.g., nausea, stomach/abdominal pain, diarrhea; (xi) urogenital problems, e.g., frequent urination, (xii) anxiety; and (xiii) depression.

1.3.1.3. *Secondary Endpoints*

The study will also evaluate various secondary endpoints, compared across the pre- and post-treatment assessment periods, to determine treatment-related effects on activity and general health status.

Specific secondary endpoints, measured pre- and post-treatment, will include:

- An assessment of hours of upright activity, and any unusual exertion or stimulation, will be recorded at the same time each day (ideally 6-8pm).
- Exploratory measures: Assessed via Fitbit Charge 2™ (measuring activity, HR and derivative parameters including resting HR, sleep level/duration, activity level/duration, steps, calories and distance, monitored continuously and summarized daily).
- Orthostatic intolerance (OI) will be assessed at Visits 1 and 6, via of measures of HR and BP and symptomatology, while in the supine, seated and standing positions.
- General health status: Assessed via the 36-Item Short Form Survey Instrument [McHorney 1994]), and vitals (measuring HR, BP, temperature, respiratory rate) at Visits 1-6.

1.3.1.4. Dosing

CT38s solution will be delivered by continuous SC infusion, via a CME T34™ programmable syringe pump), at a fixed concentration, with patient-specific dose volumes calculated to achieve the intended dose levels, specified in terms of µg/kg of body weight, or µg/kg/hour (Table 6.1).

Dose	Total Dose (µg/kg)	Priming Bolus (µg/kg)	Infusion Rate (µg/kg/h) / Duration (h)			Estimated* C _{max} (ng/ml)	Estimated* AUC (ng.h/ml)	Comment
			Initial	Escalation 1	Escalation 2			
Low	0.80	0.00	0.20 / 0:45	0.22 / 0:45	0.24 / 2:00	[proprietary data redacted]	Complete	
D1	0.11	0.00	0.03 / 0:45	0.03 / 0:45	0.03 / 2:00		No priming, no escalation	
D2	0.35	0.00	0.10 / 0:45	0.10 / 0:45	0.10 / 2:00		No priming, no escalation	

C_{max} = maximum plasma concentration, at the end of dosing; *AUC* = total area under the plasma concentration-time curve.
 * Estimated based on modeling the Phase 1 trial, in which CT38s was administered by SC bolus only and the first 2 patients dosed under this trial by SC infusion

1.3.1.4.1. CT38s Concentration

The prior Phase 1 study... [proprietary data redacted].

1.3.1.4.2. Dose Levels

Patients will be enrolled sequentially to receive either D1 or D2 doses, with at least 3 patients per dose group, and the remainder allocated determined by the tolerability to D1 and D2. In each case, the total dose will be delivered in the form of an SC infusion at a constant rate of infusion maintained for a period of 3.5 hours (~2 half-lives). This infusion dose will take place at Visit 3 (Day 29), Visit 4 (Day 31) and Visit4b, i.e., a total dose delivered over 10.5 hours.

Dosing will take place sequentially with all D1 testing taking place before D2 testing. Barring any clinically meaningful concerns with the D1 arm, including PK assessments, the D2 arm is intended to achieve higher concentrations and exposures (Table 6.1).

1.3.1.5. Dose Justification

Safety and toxicology testing of CT38 in animals [IB, Section 4] and humans [IB, Section 5], showed that the principal AEs resulting from CRF₂ stimulation were increased HR, decreased BP and decreased temperature. In animals, these effects generally correlated with ... [proprietary data redacted].

In rats, cardiovascular adjustments during stress are known to involve both CRF₁ and CRF₂ in the BNST (in the limbic system) [Oliveira 2015], while stress-induced changes in body temperature are known to occur in the hypothalamus [Vinkers 2010]. Thus, these data collectively suggest that infusions of CT38 can bring about some level of CRF₂ endocytosis within the limbic system [IB, Section 4.1.1.4]. The data further suggest that CRF₂ endocytosis... [proprietary data redacted].

The first 5 ME/CFS patients dosed under this protocol (see 6.1.2.6.), confirmed that the AEs were indeed hemodynamic, and that these occurred at substantially lower plasma concentrations than in healthy subjects (Phase 1). This apparent sensitivity of ME/CFS patients suggests that these curves may be left-shifted, and thus the amended doses seek to reduce the rate of CRF₂ stimulation.

1.3.1.5.1. Low Dose

The Low dose group (2 patients) received total doses of between 0.79 and 0.83 µg/kg at each Visit. Although this was below the MTD_b determined in Phase 1, it was associated with clinically significant hemodynamic AEs, and will not be tested further.

1.3.1.5.2. D1 Dose

The D1 dose group will receive a total dose of 0.11 µg/kg utilizing a constant infusion rate of 0.03 µg/kg/hour, repeated on each of 3 treatment days. Patients will be monitored for an additional 90 minutes (or more, as needed) after the end of infusion, before leaving the clinic.

The first 3 patients receiving the D1 dose on each of 2 separate treatment days reached maximum plasma concentrations of... [proprietary data redacted], with no evidence of carryover from the first treatment day to the second. The plasma concentrations remain below the level where hemodynamic changes were evident in the first 2 ME/CFS patients dosed... [proprietary data redacted].

1.3.1.5.3. D2 Dose

Escalation to the D2 dose group will take place provided safety and tolerability parameters for the D1 dose group support the escalation. The D2 dose group will receive a total dose of 0.35 µg/kg and utilize a constant infusion rate of 0.10 µg/kg/hour. This is projected to reach maximum plasma concentrations of... [proprietary data redacted]. Patients will be monitored for an additional 90 minutes (or more, as needed) after the end of infusion, before leaving the clinic.

It is anticipated that the revised D1 and D2 doses will be sufficient to characterize the safety, tolerability and dose-concentration relationship in ME/CFS patients. However, it might be necessary to add an additional dose, longer dosing timeframes and/or up to an additional 2 days of dosing. This will only be done following a comprehensive assessment of safety, tolerability, pharmacokinetics and efficacy.

1.3.1.5.4. Total Exposure

Long-term efficacy studies in various animal models of muscle wasting, dosed CT38 by continuous SC infusion (utilizing implanted osmotic minipumps) at doses of 100 µg/kg/day of body weight for up to 3 months in rats (5 months in hamsters). In rats, this achieved... [proprietary data redacted], with the tested animals displaying no obvious safety concerns and exhibiting robust muscle preservation. The D2 dosing paradigm is not projected to exceed total exposure of... [proprietary data redacted] ...in humans per infusion, which is several orders of magnitude below those utilized in long-term animal efficacy studies.

1.3.1.6. Dose Discontinuation

It is impossible to know the extent of any potential CRF₂ up-regulation and the related left-shift of the hemodynamic dose-response curve in ME/CFS patients. While the revised dosing paradigm is not expected to cause clinically important changes in HR or BP, these will be carefully monitored during the procedure. Baseline HR and BP measures will be made in duplicate just prior to the infusion and represent Time Zero (See Section 6.3.3.2.5). The baseline HR and BP (systolic and diastolic) will consist of the average of the duplicate readings taken in the semi-recumbent position. Dosing should be stopped in a given patient if any of the following are noted: (i) a systolic BP ≤ 90 mmHg or a ≥ 20 mmHg decrease from baseline on 3 consecutive readings; (ii) a diastolic BP ≤ 50 mmHg or a decrease ≥ 15 mmHg from baseline on 3 consecutive readings; or (iii) a resting HR ≥ 120 BPM or ≤ 45 BPM. If a patient's baseline HR or BP meet the 'stopping criteria' at baseline, the infusion must not be administered. The investigator should discuss with the medical monitor whether to bring the patient back for reassessment for study drug infusion. The time window for reassessment should not be greater than 14 days. If, after reassessment, the patient does not receive the Visit 3 infusion, then the patient should be discontinued from the study.

Lack of tolerability will be monitored in an individual patient by a careful review of the type, severity and frequency of toxicities, e.g., as described in the National Cancer Institute, Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events v3.0, 12Dec2003. Furthermore, a decrease

from baseline in either systolic BP of ≥ 20 mmHg or diastolic BP of ≥ 15 mmHg, on 2 readings 30 minutes apart will be reviewed for clinical manifestations of lack of tolerability.

1.3.2. Selection of Study Population

1.3.2.1. Inclusion Criteria

Patients who meet all of the following criteria are eligible to participate in the study:

- Provision of signed and dated informed consent form
- Ability to read, understand and speak English
- Living at an altitude between 3,500 and 5,500 feet above sea level for the past 1 year
- Willing to perform an exercise test
- Diagnosed with ME/CFS and meet the following 3 case definitions: Fukuda Research Case Definition for CFS (1994), Revised Canadian Consensus Criteria for ME/CFS (2010) and the IOM Clinical Diagnostic Criteria for ME/CFS (2015)
- Relatively stable state of illness for the individual patient over the past 3 months
- Male or female, between the ages of 18 and 60 years old
- Males or females of reproductive potential agree to remain abstinent or use (or have their partner use) 2 acceptable methods of contraception, starting from the time of informed consent through 28 days after the last dose of study drug. Acceptable methods of birth control during the study are intrauterine device, diaphragm with spermicide, contraceptive sponge, condom or vasectomy. Oral contraceptive pills may not be used as the sole method of contraception because the effect of CT38 on the efficacy of oral contraceptive pills has not yet been established
- Stated willingness to comply with all study procedures and remain available for the study duration
- Have mobile (smart) phone and access to the internet

A patient may be enrolled only once and may only receive the prescribed 2 days of study treatment once.

1.3.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in this study:

- Alternate medical or psychiatric illness that could explain the ME/CFS symptoms
- Active or uncontrolled co-morbidities which in the opinion of the PI may interfere with the ability of the patient to participate in the study. Co-morbidities may include acute infection, Crohn's disease, diabetes mellitus (Type 1 or Type 2, evidenced by a history of hemoglobin A1C > 7 at any time), Guillain-Barre syndrome, lupus, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, or other such diseases that may be exclusionary. Particularly conditions or medications that cause immunodeficiency or immunosuppression will be excluded. Examples of such conditions can be found in the tables "Causes of Secondary Immunodeficiency" and "Some Drugs that Cause Immunosuppression" in the "Merck Manual"
- Pregnancy, or while breast feeding. Women should not be enrolled within 6 months of giving birth and within 3 months of cessation of breast feeding
- A Body Mass Index > 35
- Cigarette smoker or former smoker who has smoked within 6 months of the start of the study
- Living at an altitude that is more than 1,000 feet (lower or higher) from the study site (which is 4,500 feet above sea level)

- History of:
 - Major depression with psychotic or melancholic features before the diagnosis of ME/CFS, or active depression (major depression with psychotic or melancholic features) as determined by self-report
 - Untreated endocrine diagnoses including hypothyroidism (Hashimoto's, etc.), Grave's disease, adrenal insufficiency, hypogonadism (testosterone deficiency), diabetes mellitus or insipidus
 - Acute infection within the past 30 days
 - Within the last 3 years, any significant head injury, e.g., concussion with loss of consciousness, brain surgery, an automobile accident with head/neck injury, other traumatic brain injury
 - A supra-ventricular tachycardia or ventricular tachycardia, e.g., atrial fibrillation or flutter, paroxysmal atrial fibrillation, junctional tachycardia, ventricular tachycardia
 - Severe baseline hypotension defined as rested sitting systolic BP < 100 mmHg or rested sitting diastolic BP < 60 mmHg. Severe baseline tachycardia (HR > 100 bpm) or bradycardia (\leq 45 bpm).
 - Renal impairment based upon the local lab normal estimated glomerular filtration rate (eGFR) (drug is cleared by passive renal filtration)
 - Known hypersensitivity or clinically significant allergies to... **[proprietary data redacted]** (both excipients in the drug product)
 - Substance abuse in the past 12 months as determined by self-report
- Improvement in overall ME/CFS symptoms as a result of any treatment intervention in the past 3 months
- Current treatment with medications that interact with pathways involving: (i) 5HT (e.g., selective 5HT re-uptake inhibitors or SSRIs, 5HT and norepinephrine re-uptake inhibitors or SNRIs, tricyclic antidepressants, monoamine oxidase inhibitors, triptans); (ii) norepinephrine (e.g., adrenergic agonists or antagonists, norepinephrine re-uptake inhibitors, norepinephrine and dopamine re-uptake inhibitors); (iii) dopamine (e.g., norepinephrine and dopamine re-uptake inhibitors); and (iv) cortisol (e.g., oral glucocorticoids, fludrocortisone). Prior withdrawal of medications, see Section 6.3.4.7.
- Prior treatment with
 - Short-term (< 2 weeks) antiviral or antibiotic medication or flu shot within the past 4 weeks
 - Long-term (> 2 weeks) antiretrovirals within the past 12 months
 - RituximabTM within 6 months
 - Any new prescription drug or herbal remedy within 2 weeks prior to the onset of the trial
- Current participation in another clinical treatment trial

1.3.2.3. Removal of Patients from the Study

Withdrawn patients are those who do not complete all evaluations and procedures outlined in the protocol because of one of the following: an AE; significant protocol deviation that, in the opinion of the PI, may compromise the study results; voluntary withdrawal; or withdrawal at the PI's discretion.

If possible, any patient who is withdrawn from the study will have, at the time of withdrawal, all exit procedures performed (see below). All clinically significant findings will be followed until resolved to the satisfaction of the PI in consultation with the Medical Monitor. If patients withdraw before or during treatment, the clinical team will seek to enroll additional patients.

1.3.3. Study Procedures

1.3.3.1. Schedule of Events

The complete schedule of study procedures is presented in Table 6.2. While efforts will be made to comply with the schedule of events and descriptions below, the precise timing may vary, except for Visit 3, Visit 4 and Visit 4b, which each must be separated by at least 48 hours and no more than 96 hours. The pre-treatment assessment period (between Visit 1 and Visit 3) and the post-treatment assessment period (between Visit 4b and Visit 6) should each be at least 4 weeks.

1.3.3.2. Study Specific Procedures

1.3.3.2.1. Visit 1 (Day 1)

During the recruitment period up to 18 ME/CFS patients will be screened according to the inclusion/exclusion criteria with the goal of enrolling 6 patients per dose-level. Qualified patients will be invited to participate in the study.

At Visit 1, patient eligibility will be confirmed and the following will be conducted:

- Completed and signed Informed Consent Form
- Medical history, including any information on the event that triggered ME/CFS, alcohol, tobacco or nicotine-containing product use, illicit drug use, etc.
- Medication history, including prescription drug or herbal remedy within the past 3 months and non-prescription drug or vitamin within the past 2 weeks
- Physical examination, including height and weight
- Vital signs, including HR, BP (measured twice after 5 minutes sitting), oral temperature, respiratory rate
- Completed SF-36 (done prior to OI testing, see below)
- Urine pregnancy / drug screen
- Blood test (to establish eGFR, as well as standard chemistry panel and complete blood count). If the following laboratory blood tests have not been done within 3 months of the screening visit (or the results are not available) then these blood tests should be ordered as well: Lipid panel (T.Chol, HDL, LDL and TG), Total and Free Testosterone (males), ESR, CRP, Rheumatoid Factor, ANA, TSH and Free T4, Vitamin D 25-OH, Ferritin, Creatine Kinase, hemoglobin A1C, PSA (males).
- OI testing: Patients will lay supine for 5 minutes with HR and BP recorded in the last minute of supine rest. Patients will then sit upright with legs hanging over the side of the bed for 1 minute, with HR, BP and any new symptoms developing during the seated position (e.g., dizziness, visual disturbances, palpitations) recorded at the end of the 1-minute period. Patients will then stand for 10 minutes near the bed and HR, BP and any new symptoms will be recorded at 2, 5 and 10 minutes post standing. Ideally, HR should be monitored continuously with a pulse oximeter or other such device. Patients developing any symptoms suggestive of hypotension at any stage, should be rested in either the seated or supine position.

Before leaving the clinic, patients will be assigned a patient number and Fitbit Charge 2™ for continuous monitoring (activity, sleep and HR) throughout the trial..

1.3.3.2.2. Pre-Treatment Assessment Period (Days 1-28)

In the 4-week pre-treatment assessment period, patients will utilize the wearable Fitbit Charge 2™ to record activity, sleep-related data and HR, and complete the daily VAS (online), and daily hours of upright activity (online). Patients will also record any changes in medication use, any AEs and other qualitative observations (online).

1.3.3.2.3. Visit 3 (Day 29)

At Visit 3 (Day 29) patients will complete SF-36 and undergo a brief physical exam, recording vitals and any patient-recorded changes in medications, AEs and other qualitative observations during the pre-treatment recovery period. A urine pregnancy test will be performed prior to study drug administration. In addition, patients will have an intravenous catheter placed in the arm to facilitate blood sampling for PK assessment. Following this, the study drug will be administered as outlined above, beginning at approximately 10am.

Patients should be semi-recumbent before and during the infusion procedure. Prior to the infusion, duplicate measures of HR and BP should be made after 10 minutes in the semi-recumbent position. The duplicate measures should be averaged and the average of the HR, systolic and diastolic BP will represent baseline (Time Zero). These baseline values should be recorded and the infusion stopping criteria (Section 6.3.1.6) should be annotated prior to the start of the infusion for reference purposes. During the procedure, HR and BP will be monitored every 15 minutes throughout the infusion period and for a minimum of 90 minutes post infusion. The post infusion vital sign monitoring may be prolonged as appropriate until clinically stable. PK samples will be obtained prior to the onset of study drug administration, and at 45 minutes, 90 minutes, 210 minutes (after stopping infusion) and at 300 minutes (before the patient is allowed to go home). All AEs will be assessed and recorded as well as the need for any medications. Provided patients are clinically stable they may leave the clinic at 2 hours post-infusion.

1.3.3.2.4. Visit 4 (Day 31)

At Visit 4 (Day 31) patients will undergo a brief physical exam, recording vitals and any patient-recorded changes in medications or AEs. Following this, the study drug will be administered as outlined above (see Visit 3), beginning at approximately 10am.

Both before and during the infusion procedure, HR and BP will be monitored exactly as described for Visit 3, and blood samples for PK assessment will be obtained, per the schedule at Visit 3. All AEs will be assessed and recorded as well as the need for any medications.

1.3.3.2.5. Visit 4b (Day 33)

At Visit 4b (Day 33) patients will undergo a brief physical exam, recording vitals and any patient-recorded changes in medications or AEs. Following this, the study drug will be administered as outlined above (see Visit 2), beginning at approximately 10am.

Both before and during the infusion procedure, HR and BP will be monitored exactly as described for Visit 3, and blood samples for PK assessment will be obtained, per the schedule at Visit 3. All AEs will be assessed and recorded as well as the need for any medications. Treatment Period (Days 29-36)

Throughout the 1-week treatment period (including treatment days), patients will utilize the wearable Fitbit Charge 2™ to record activity, sleep-related data and HR, and complete the daily VAS (online), and daily hours of upright activity (online). Patients will also record any changes in medication use, any AEs and other qualitative observations (online).

1.3.3.2.6. Post-Treatment Assessment Period (Days 36-63)

Throughout the 4-week post-treatment recovery period, patients will utilize the wearable Fitbit Charge 2™ to record activity, HR and sleep-related data, and complete the daily VAS (online), and daily hours of upright activity (online). Patients will also record any changes in medication use, any AEs and other qualitative observations (online).

1.3.3.2.7. Visit 6 (Day 64)

At Visit 6 (Day 64), patients will undergo a final checkup, including physical examination, recording vitals and any updates to patient history. Patient will be required to complete SF-36, followed by OI testing conducted exactly as at Visit 1. All AEs will be assessed and recorded as well as the need for any medications.

1.3.3.3. Safety Assessments

Specific safety parameters and procedures will be as follows:

- Clinical observation and assessment of AEs
- Subjective symptoms and complaints via individual interviews
- Vital signs, including HR, BP, oral temperature and respiratory rate. Abnormal BP readings will be treated and followed as appropriate
- Physical examination as required

When an AE is suspected, all relevant evaluations will be carried out and appropriate treatment provided. Additional follow-up will be performed as necessary, recorded in the patient's source documents, with the results provided to the PI. Patients who experience any clinically significant AE will remain under medical supervision until the PI, in consultation with the Medical Monitor, deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

Note that prior to dose, only serious, procedure-related AEs will be captured on the AE case report form). For AE definitions and reporting requirements, see below.

1.3.4. Study Agent

1.3.4.1. Formulation, Appearance, Packaging, and Labeling

All study medication will be supplied by Cortene in sterile single-use vials.

CT38 Concentrate will be supplied in Schott 6R vials containing 1 ml of 1 mg/ml concentration... [proprietary data redacted].

Diluent for CT38 Concentrate will be supplied in Schott 6R vials containing 6 ml of... [proprietary data redacted].

1.3.4.2. Product Storage and Stability

The unopened vials of CT38 Concentrate and Diluent for CT38 Concentrate are to be stored at -20°C, which ensures at least 18 months of stability.

1.3.4.3. Preparation

Prior to use, CT38 Concentrate must be diluted, using the Diluent for CT38 Concentrate, to produce the sterile solution intended for patient dosing ("CT38 Solution")... [proprietary data redacted].

Following overnight thawing (at 5°C)... [proprietary data redacted] ...of respectively CT38 Concentrate and Diluent for CT38 Concentrate, are drawn into the syringe intended for patient dosing. The resulting CT38 Solution for injection/infusion must be refrigerated at 5°C for no more than 24 hours prior to use. Detailed instructions will be provided to the site directly.

1.3.4.4. Management of Clinical Supplies

The PI will have overall responsibility for the use of the study medication, and will not permit use other than as directed by this protocol. The PI or designee will provide a signed acknowledgment for receipt of the study medications and a signed acknowledgment for return of study medication containers and unused study medication.

Qualified study center personnel must receive study drug deliveries, record the receipt, and assure that the study drug is handled and stored safely and properly. The invoice must be reconciled against the vials received. Any extra/damaged drug product vials will be destroyed at the study center as instructed and documented by Cortene.

A site designated person and a dedicated assistant, using the accompanying dosing instructions, will prepare doses for each patient. Preparation must be documented and checked. Copies of all invoices and dispensing records for the study drug must be kept at the study center as part of required study documentation. At the end of the study, the study center must be able to reconcile delivery records with records of study drug received, dispensed and returned. An account must be given of any discrepancies.

Upon completion or termination of the study, remaining drug substance and administration materials will be returned to Cortene, unless otherwise instructed by Cortene.

1.3.4.5. *Treatments Administered*

Study drug will be administered as described above. The site will prepare the doses using only materials provided by Cortene for this study. Dosing solutions will be prepared using empty sterile syringes, according to the Dose Preparation Form instructions provided by Cortene. All parenteral products will be inspected visually prior to administration. The solution should be administered only if it is clear, colorless, and free of visible particulate matter.

1.3.4.6. *Treatment Compliance*

The prescribed dosage and mode of administration may not be changed. Any departures from the intended regimen will be recorded.

1.3.4.7. *Prior and Concomitant Therapy*

During study participation, patients will be prohibited from taking any new prescription medications unless required to treat an emergency, or as explicitly approved by the PI and Medical Monitor. Examples of these drugs include amphetamines (e.g., Adderall, armodafinil, modafinil and methylphenidate). Short acting benzodiazepines and gabapentin use are allowed.

Patients who have been withdrawn from medications that interact with the 5HT, norepinephrine or dopamine signaling pathways, should have been withdrawn at least 6 weeks prior to screening and should have had 4 weeks of relative stability prior to screening in the opinion of the investigator. If patients have been recently withdrawn (at least 6 weeks) from oral corticosteroids, the investigator should be satisfied that the underlying illness for which these medications were used is stable and the risk of having to reinstate the corticosteroids over the period of the trial is low.

1.3.5. *Statistical Methods*

1.3.5.1. *Statistical Analysis Plan*

Descriptive statistics such as means, medians, standard deviations, and interquartile ranges will be generated for all continuous variables, while frequency tables will be provided for categorical and discrete variables. In addition, other exploratory statistical analyses, including stratification for disease severity and other variables, will also be performed. A significance level (p-value) of less than 0.05 will be used for all statistical tests.

1.3.5.2. *Power and Sample Size Considerations*

Given that this is a proof of concept study, no formal power calculations have been made. The study seeks to enroll up to 18 patients. Summary statistics will be performed with comparison made between pre- and post-treatment assessment periods using appropriate statistical tests.

1.3.6. *Data Quality Assurance*

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Site initiation call
- Case report form review against source documents
- Data management quality control checks
- Statistical quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final report

1.4. Investigator's Obligations

This study will be conducted in accordance with this protocol, the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice, 1997, the US Code of Federal Regulations Title 21 parts 50, 56, and 312, and the ethical principles that have their origin in the Declaration of Helsinki.

1.4.1. Institutional Review

The PI will not begin the study until the protocol and informed consent form have been approved by the Institutional Review Board (IRB). The IRB will also review and approve all advertisements. The IRB's approval will be documented in writing and sent to the PI. The PI will forward a copy of the IRB approval document to Cortene. Any amendments to the protocol must also be approved in writing by the IRB, prior to implementation by the PI, except where necessary to eliminate an immediate hazard to study patients.

1.4.2. Patient Consent

Each patient must sign and personally date a study-specific informed consent form to participate in the study. This consent form will comply with all applicable regulations governing the protection of human patients. The basic elements of informed consent are specified in the US Code of Federal Regulations Title 21 parts 50.25 and 50.27, and the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

The PI will obtain the IRB's written approval of the written informed consent form to be provided to the patients, including approval of all revisions. Prior to the start of the study, the PI or an authorized staff member will inform patients about the nature of the study. Patients will have the opportunity to inquire about details of the study and to decide whether to participate. Patients will be instructed that they are free to withdraw their participation in the study at any time without penalty or loss of benefits to which they are otherwise entitled. The PI will inform patients of new information that may be relevant to the patients' willingness to continue participation in the study.

The PI will provide each patient with a copy of the signed and dated consent form and will document in the patient's source documents that informed consent was given.

1.4.3. Data Collection

1.4.3.1. Case Report Forms

This study will utilize online case report forms (using REDCap).

1.4.3.2. Source Documents

The PI will prepare and maintain adequate and accurate source documents (medical records, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient treated with the study drug.

The PI will allow Cortene representatives, contract designees, and authorized regulatory authority inspectors to have direct access to all documents pertaining to the study.

1.4.4. Adherence to Protocol

By signing the Protocol Approval Signature Page of this protocol, the PI confirms in writing that he/she has read, understands, and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and applicable regulatory requirements.

1.4.5. Reporting Adverse Events

1.4.5.1. Safety Definitions

AE: Any unfavorable or unintended sign, symptom, or disease that appears or worsens in a patient during the period of observation in a clinical study. The AE may be any of the following:

- A new illness
- An exacerbation of a sign or symptom of the underlying condition under treatment or of a concomitant illness, unrelated to participation in the clinical study, or an effect of the study medication
- A combination of one or more of the above factors

No causal relationship with the study medication is implied by the use of the term “adverse event.” An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. (If the event fits the serious criteria, such as an extended hospitalization, it will be considered an SAE.) Conditions leading to unplanned surgical procedures may be AEs.

When an AE occurs after written informed consent has been obtained but before the first dose of study drug, the AE will be considered a non-treatment-emergent AE. Only serious non-treatment-emergent AEs that are related to study procedures will be collected. An AE that occurs from the time the patient receives his/her first dose of study drug until his/her exit from the study will be considered a treatment-emergent AE. All treatment-emergent AEs will be collected.

Immediately Reportable Adverse Event (IRAE) include all SAEs (as listed below), AEs that result in a patient’s withdrawal from the study, and designated program-specific AEs, and must be reported to Cortene within 24 hours of the study center being informed.

SAE: As provided by the ICH criteria, any AE that:

- results in death
- is life threatening (Note, the term "life threatening" refers to any AE that, as it occurs, puts the patient at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe).
- results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the patient's underlying medical condition prior to entry into the study)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect in the offspring of a patient
- is judged to be medically significant (Note, a medically significant AE is a medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or require intervention to prevent one of the outcomes listed above. Medical and scientific judgment should be exercised in deciding whether other AEs appropriately meet these criteria and are immediately reportable to Cortene. Examples of such medical events include allergic bronchospasm that requires intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in in-patient hospitalization).

When completing appropriate forms for reporting the AE, the PI will be asked to assess the AE as follows:

Severity of AE: Refers to the extent to which an AE affects the patient’s daily activities. Severity will be categorized according to the following criteria:

- Mild: Normal activities unaltered
- Moderate: Normal activities altered
- Severe: Unable to undertake normal activities.

The term “severity” is used to describe the intensity of an event (as in mild, moderate, severe); the event itself may be of relatively minor medical significance, such as a severe headache. This is not the same as “serious.” Seriousness, not severity, serves as the guide for defining regulatory reporting obligations.

Causality of AE: Refers to the relationship of the AE to study drug. Causality will be categorized according to the following criteria:

- **Doubtful:** There is no medical evidence to suggest that the AE may be related to study drug usage, or there is another more probable medical explanation
- **Possible:** There is medical evidence to suggest that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause
- **Probable:** There is strong medical evidence to suggest that the AE is related to study drug usage

1.4.5.2. Reporting Forms

In this study AEs will be reported via the case report form.

All AEs (AE log of case report form): The AE log is part of the case report form and is used to collect information on the following:

- All treatment-emergent AEs (serious and non-serious)
- Serious, non-treatment-emergent AEs related to study procedures

Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

IRAEs: All known information regarding the IRAE must be recorded on the AE log of the case report form and all other case report forms updated or completed as necessary. Case report forms that must be completed for all IRAEs are: patient accountability, study drug accountability, demographics, medical history, and concomitant medications. This information must be completed within 24 hours of the study center being informed of the IRAE.

1.4.5.3. Adverse Event Reporting Contacts

For questions regarding IRAEs, or to notify Cortene of an IRAE in the event of technical failure, the PI should contact the Medical Monitor.

1.4.5.4. Unintended Pregnancy

Patients will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Patients who become pregnant or who suspect that they are pregnant during the study must report the information to the PI and discontinue study drug immediately. Patients whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator.

The study consent allows the PI to follow a patient or partner pregnancy until completion or termination. The patient will be asked to provide information on the outcome of their or partner pregnancy, including early termination. The PI or study staff may share this information with Cortene and the IRB.

1.4.6. Records Retention

The PI must maintain essential study documents (protocol and amendments, source documentation corresponding to all information contained in the case report form, signed informed consent forms, relevant correspondence, test results, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private

practice in which the study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same time period. Custody of the records may be transferred to another responsible party, acceptable to Cortene, who agrees to abide by the retention policies. Written notice of transfer must be submitted to Cortene. The PI must contact Cortene prior to disposing of any study records.

1.4.7. Publications

The PI agrees that all data, calculations, interpretations, opinions, and recommendations regarding the study will be the property of Cortene. The PI agrees to consider the results as information subject to confidentiality and use restrictions.

1.5. Study Administration**1.5.1. Management of Protocol Amendments and Deviations**

With the exception of an emergency situation, implementation of any change in the protocol that affects the safety of the patients, the scope of the investigation, or the scientific quality of the study will not be permitted until Cortene, the PI and the IRB responsible for review and approval of the study have reviewed and approved the amendment.

Implementation of changes that do not affect the safety of the patients, the scope of the investigation, or the scientific quality of the study cannot be made until the protocol changes are reviewed and approved by Cortene and the PI. The IRB must be notified of these protocol changes.

The PI will not deviate from the protocol without prior written approval from Cortene. In the event of an emergency, the PI shall implement any medical procedures deemed appropriate. However, all such procedures must have written documentation and be promptly reported to Cortene.

1.5.2. Study Termination

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the FDA. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy PI, IRB and FDA.

The study is considered terminated upon completion of all patient treatments and evaluations.

1.5.3. Final Report

The PI will review and sign the final report at the conclusion of this clinical study.

1.5.4. Patient-Related**1.5.4.1. Patient Identification**

Upon their enrollment in the study, all patients will be assigned a unique study number. The link between the patient's study number and their identifiers will be kept in a password-protected database

that only the study team can access, in compliance with the Health Insurance Portability and Accountability Act of 1996.

1.5.4.2. Patient Payments

Patients will be compensated for their time at a rate of US\$10/hour, for parking and transportation at US\$10/visit (5 separate study visits). Patients' time will include screening/enrollment at Visit 1 (4 hours), treatment at Visit 3, Visit 4 and Visit 4b (each 7 hours), close-out at Visit 6 (2 hours), and data entry over the course of the study (18 hours), so a total of 45 hours. This amounts to a total compensation of \$500 provided all study visits and outcome measures are completed, which will be paid after the completion of the Visit 6. Patients only completing through Visit 1, Visit 3, Visit 4 and Visit 4b will receive respective payments of \$50, \$150, \$250 and \$350 in total.

1.5.4.3. Insurance

If health complications due to study procedures arise, the PI and the research study staff will assist the patient in obtaining appropriate medical treatment. In the event that the patient has an injury or illness that is directly caused by his or her participation in this study, reimbursement for medical expenses (e.g., ambulance, hospital, professional nursing, dental, medical, surgical, imaging, first aid and funeral services) will be sought from Cortene's insurer.

If the patient's medical expenses related to such an injury are not covered by Cortene's insurer, the patients may be responsible for these costs.

1.5.4.4. Strategies for Recruitment and Retention

The study will seek to recruit a total of 18 ME/CFS patients within Salt Lake City and the surrounding areas.

Potential cases will be identified/recruited as follows.

- PI's current and prior ME/CFS patients may be eligible for the study. PI will generate a list of male and female patients who are between ages 18 and 60. These patients will be called on the telephone to determine interest in participating in the study, and if interested, will be screened for eligibility, and if eligible, invited to schedule the first study visit.
- PI's waiting list of ME/CFS patients will be called, and if interested, will be screened for eligibility, and if eligible, invited to schedule the first study visit.
- Study flyers will be posted at PI's clinic with the research coordinator's contact information. Patients who call will be screened for eligibility, and if eligible, invited to schedule the first study visit.
- Advertisements for the study will be posted on the Bateman Horne Center's website. Potential patients who contact the research coordinator will be screened for eligibility, and if eligible, invited to schedule the first study visit.
- The study team will also contact other providers who see ME/CFS patients. Such providers may refer patients to the study and may also post the study flyers in their offices and advertisements on their websites. Interested patients who contact the research coordinator will be screened for eligibility, and if eligible, invited to schedule the first study visit.
- Patients will also be recruited using the website ResearchMatch, a registry with over 79,000 patients, created by the Clinical & Translational Science Awards (CTSA) Consortium and funded by the National Center for Research Resources. Once recruitment access has been approved by the site (with evidence of IRB-study approval), the research coordinator will search for matches among the patient profiles within the system and send a recruitment message to potential matches through ResearchMatch. For those patients who authorize ResearchMatch to release their contact information, the research coordinator will contact the patient to set up a telephone screening. Such patients will be screened for eligibility, and if eligible, invited to schedule the first study visit.

1.6. References

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