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Phase I, randomized, double-blind, placebo controlled study to determine the safety, tolerability, and pharmacokinetics of a single escalating dose and repeated doses of CN-105 in healthy adult subjects

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Abstract

Spontaneous intracranial hemorrhage (ICH) remains a devastating stroke subtype, affecting as many as 80,000 people annually in the United States and associated with extremely high mortality. In the absence of any pharmacological interventions demonstrated to improve outcome, care for patients with ICH remains largely supportive. Thus, despite advances in the understanding of ICH and brain injury, there remains an unmet need for interventions that improve neurologic recovery and outcomes. Recent research suggesting inflammation and APOE genotype play a role in modifying neurologic outcome after brain injury has led to the development of an APOE-derived peptide agent (CN-105). Preclinical studies have demonstrated that CN-105 effectively down regulates the inflammatory response in acute brain injury, including ICH. Following Investigational New Drug (IND) enabling studies in murine models, this first in-human single escalating dose and multiple dose placebo-controlled clinical trial was performed to define the safety and pharmacokinetics (PK) of CN-105. A total of 48 subjects (12 control, 36 active) were randomized in this study; all subjects completed the study. No significant safety issues were identified with both dosing regimens, and PK analysis revealed linearity without significant drug accumulation. The median half-life in the terminal elimination phase of CN-105 following a single or repeated dosing regimen did not change (approximately 3.6 hr). With the PK and preliminary safety of CN-105 established, the drug is now poised to begin first in disease phase 2 clinical trials in patients with ICH who urgently need new therapeutic options.

Keywords

intracerebral hemorrhage (ICH); brain injury; neuroinflammation; neuroprotection; apolipoprotein E (apoE); pharmacokinetics

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INTRODUCTION

Acute brain injury resulting from cerebrovascular diseases and trauma is associated with extremely high mortality and morbidity [1,2]. Despite advances in our understanding of basic cellular and molecular mechanisms associated with primary and secondary neuronal injury, no effective neuro-protective pharmacological interventions have improved functional outcomes [3,4]. Supportive medical care remains the mainstay of management for patients with acute brain injury and mortality rates for many of these injuries have not improved in the last 2 decades [2,5,6]. There is a clear and urgent unmet clinical need for neuroprotective therapeutics for acute brain injury.

Traditionally, new therapeutic strategies have focused on our increased mechanistic understanding of disease-specific pathophysiology. However, despite these important disease-specific differences, the neuroinflammatory response, characterized by glial activation and release of mediators of inflammation, neuronal excitotoxicity, and oxidative stress serve as a common denominator that exacerbates secondary neuronal injury in a variety of acute and chronic neuropathology [7]. Moreover, in the setting of acute brain injury, neuroinflammation plays an important role in mediating tissue injury for days after the initial insult [8–10]; this has the potential to lengthen the therapeutic window as compared to strategies that solely target excitotoxicity. Thus, a therapeutic strategy that targets maladaptive neuroinflammatory responses holds promise in the treatment of diverse forms of brain injury. Apolipoprotein E (apoE) is an endogenous brain protein synthesized in response to brain injury and exists in humans as 3 common protein isoforms, designated apoE2, apoE3, and apoE4, which differ by single amino acid substitutions at residues 112 and 158 [11]. Isoform-specific protective effects on endogenous neuroinflammatory responses have been observed in humans [12,13] and demonstrated in preclinical models of brain injury [14–16]. Mechanisms by which apoE reduces neurologic inflammation have been demonstrated through specific receptor interactions [17–19] and down-regulation of microglial activation [20,21].

Previous studies from our lab and others have demonstrated that apolipoprotein E (apoE), a 299 amino acid protein produced within the brain modifies neuroinflammatory responses by downregulating glial activation and release of inflammatory mediators. However, apoE holoprotein's therapeutic potential is limited, as it does not cross the blood brain barrier (BBB). To address this limitation, we have developed apoE mimetic peptides derived from the helical receptor binding region of apoE. These peptides have been demonstrated to improve histological and long term functional outcome in preclinical models of intracerebral hemorrhage (ICH) [22,23], traumatic brain injury [24–27], ischemic stroke [28,29], subarachnoid hemorrhage [30,31] and spinal cord injury [32,33].

Recently, we have selected CN-105, an apoE-mimetic pentapeptide derived from the receptor binding face of apoE (Figure 1), as the lead candidate for further development based on its profile in *in vitro* cell culture models of neuroinflammation and neuroprotection, in *vivo* efficacy in preclinical models of intracranial hemorrhage [34], stroke, and acute brain injury and preclinical safety profile[34]. Results from the rodent and beagle Good Laboratory

Practice safety and toxicology studies demonstrated that repeated intravenous administration of CN-105 at 5 mg/kg/dose (100-fold the therapeutic dose identified in preclinical efficacy studies), four times per day (20 mg/kg/day) for 14 days was well-tolerated, and 20 mg/kg/day was identified as the no observed-adverse effect-level (NOAEL) in these studies. Based upon these promising preclinical results, the decision was made to further develop CN-105 for the treatment of human acute brain injuries.

CN-105 has never been evaluated in humans and the safety and pharmacokinetics (PK) have not been defined, and the current first-in-human (FIH) study represents the first clinical translation of this molecule to a clinical population.

METHODS

The protocol was approved by the FDA under an Investigational New Drug Application and by the Duke University Institutional Review Board. Written informed consent was obtained for each volunteer prior to performing study-related procedures.

Eligibility Criteria

Healthy male and female volunteers aged 18–50, with BMI ranging 18–33 kg/m^2, and weight of at least 50 kg were eligible for the study. Volunteers were required to have adequate peripheral vein access, no exposure to prescription medication (except contraception) or over the counter (OTC) medications or herbal/vitamin supplements (except acetaminophen ≤ 1 g/day and stable, non-glucocorticoid treatment of seasonal allergies) in the 7 days prior to study entry, no exposure to nicotine-containing products for ≥ 6 months, no current or recent (within 2 years) history of alcohol or drug abuse, caffeine consumption ≤ 3 cups of coffee per day, ability to comply with medically acceptable contraception or prior history of surgical sterilization, and no history of recent (30 days cellular and 90 days acellular) blood donation. Pregnant or lactating females and volunteers with significant medical or psychiatric illness by history or examination that would influence study results or preclude informed consent and study compliance were excluded.

Study Design

This was a Phase I, single center, randomized, double-blind, placebo controlled study to determine the safety, tolerability and pharmacokinetics (PK) of a single ascending dose (SAD) and repeated doses of intravenous CN-105 in healthy adults. In the SAD portion of this FIH study, 8 participants were randomized to CN-105 or saline control (6 active: 2 control) at 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg administered over 30 minutes. Intermittent weight based dosing was supported by preclinical animal models and was felt more practical in a clinical setting than a continuous intravenous dose[34]. The maximum dose in the study was the highest dose allowed by the U.S. Food and Drug Administration (FDA). Since this was a FIH study, an interim PK analysis was planned during the SAD portion of the study to determine the optimal PK sampling timepoints. In the repeat dose cohort 8 participants (6 active: 2 control) were randomized to receive repeated infusions of CN-105 over 30 minutes every 6 hours for 72 hours.

Data Monitoring Committee

A Data Monitoring Committee was used to evaluate safety and tolerability with the dose escalation cohorts and to select the final dose for the repeated dose cohort. Doses were escalated in successive cohorts unless one participant experienced an adverse effect of Severe Grade or two participants reported the same adverse effect of Moderate Intensity that was considered probably related to the study drug.

Safety evaluations

During and following dosing, safety and tolerability endpoints included reported adverse events (AEs), changes in vital signs, physical examination findings, ECG, and clinical laboratory tests (hematologic, chemistry, urinalysis).

Pharmacokinetic Sampling

During the SAD cohorts, blood samples were taken at 15 minutes prior to start of dosing and at 0.083, 0.167, 0.5, 1, 2, 4, 8, 12 and 24 hours from the start of dosing. Urine samples were obtained prior to dose administration and then pooled samples (0–3, 3–6, 6–8, 8–12, 12–24 hours) were collected from the start of dosing. Interim PK analysis after the second (0.03mg/kg) cohort resulted in removal of a 168 hour blood sample and addition of a urine sample from 8–12 hours. For repeat dose participants, blood samples were taken 15 minutes hour prior to start of dosing and then at 0.083, 0.167, 0.5, 1, 2, 4, 5-<6 hours for the first 2 doses and within 1 hour prior to each dose thereafter. Blood samples were also collected at 0.083, 0.167, 0.5, 1, 2, 4, 5-<6 and 12 hours after the last dose.

Plasma and urine drug concentrations were determined by MPI (Mattawan, MI). Plasma were stored in 1% HALT with K2EDTA at −70° Celsius before they were ready to be analyzed. Liquid chromatography-tandem mass spectrometry analysis was performed using a positive Turbo IonSpray® interface on a Sciex API-3000 (Applied Biosystems, Foster City, CA) and multiple reaction monitoring. The analytical range was 1.00 ng/mL to 1,000 ng/mL. The assay precision in quality-control samples was < 20% for the lowest limit of quantitation and < 15% for all other concentrations.

Pharmacokinetics and Safety Analysis

Individual plasma concentration versus time profiles of CN-105 for SAD and repeat doses were used to generate PK parameters using non-compartmental analysis. The noncompartmental PK analysis was performed in Phoenix WinNonLin (version 6.3, Pharsight Corporation) using concentration versus time data obtained for CN-105. All plasma concentrations below the quantitation limit were assigned a value of zero. For both SAD and repeat dose cohorts, the peak drug concentration (Cmax) and time of peak concentration (Tmax) were obtained from the observed data. For the SAD cohort, AUC from zero to last measurable concentration ($AUC_{0\text{-last}}$) and AUC from 0 to infinity ($AUC_{0\text{-}\infty}$) and elimination half-life ($t_{1/2}$) were calculated. For the repeat dose cohort, AUC from zero to 6 hours (AUC_{TAU}) was assessed for CN-105. $AUC_{0\text{-last}}$ and AUC_{TAU} were calculated using the trapezoidal rule. In addition, the $AUC_{0\text{-}\infty}$ was calculated from $AUC_{0\text{-last}} + Ct/\lambda z$ where Ct is the last measurable concentration, and λz is the terminal elimination rate constant calculated by fitting 3 points to a linear regression. The half-life ($t_{1/2}$) was calculated as

0.693/λz. At least 3 time points with measurable plasma concentrations were required for the calculation of AUC_{last} and at least 3 time points (of which the first time point must be greater than Tmax) with measurable plasma concentrations were required for the calculation of λ_Z. Total body clearance (CL) was calculated as $Dose/AUC_{\infty}$. The volume of distribution (V) was calculated as $V = CL/\lambda z$.

Primary analysis of safety and tolerability using vital signs, ECG, clinical laboratory results and AEs was performed using descriptive statistics. Categorical variables were analyzed as counts and percentages, while continuous variables were presented as means and standard deviations or medians and interquartile ranges. Statistical analyses were performed using Version 9.4 (or newer) of SAS® (Cary, NC) on an Unix operating system or Stata 13.1 (College Station, TX).

RESULTS

Demographics

Sixty-six adults were enrolled, and 48 completed the clinical trial. The study population was predominantly male (79%) and African American (69%) (Table 1). These demographics were similar between the placebo and treatment groups.

Safety and Tolerability

Among the 48 subjects in this study, 23 (47%; 18 active: 5 placebo) experienced an AE. A total of 18 subjects (37.5%) experienced a treatment-emergent AE, 4 (33.3%) in the placebo group and 14 (38.9%) in the CN105 group. Bradycardia and headache were the most common treatment-emergent AEs. A total of 6 (12.5%) subjects experienced bradycardia, 2 (17%) in the placebo group and 4 (11%) in the CN-105 group; a total of 2 (4%) subjects reported headache, 0 (0%) in the placebo group and 2 (6%) in the CN-105 group. The bradycardia in most cases was not treatment emergent and likely related to the study population of young healthy volunteers. No Serious Adverse Events or deaths occurred. No concerning changes were observed in serial ECG, vital signs or clinical laboratory tests.

Pharmacokinetic summary

All subjects receiving CN-105 (n = 36) had evaluable PK data and there were no missing data. For the single ascending doses, exposure and PK parameters are summarized in Table 2. Following i.v. infusions, concentrations of CN-105 in plasma declined in a polyphasic manner, as shown in the mean concentration of drug vs. time plot (Figure 2). A short distribution phase was seen immediately post-infusion. A dominant β phase characterized much of the profile and exhibited log-linear behavior. At higher doses, an additional longer γ phase was present post-dose at low concentrations. PK parameters for the single ascending dose regimens are summarized in Table 2. The volume, clearance and half-life remained relatively constant over the range of doses evaluated. The mean of Cmax and AUC parameters plotted versus dose in Figure 3A and 3B were well represented by linear regression lines ($r^2 > 0.99$) and consistent with dose proportionality.

PK parameters for the multiple dosing regimen are summarized in Table 3. The median (range) terminal elimination half-life after the 13th dose was 3.6 hours (3.4 – 7.1). There was no significant accumulation of CN-105 as evidenced by the relatively constant AUC_{TAU} ratios between the time points (Table 4), which is shown graphically in Figure 4. Trough concentrations reached a stable plateau by 20 hrs (Figure 4), and a steady state was achieved within the first 24 hours.

DISCUSSION

This Phase I, single-center, randomized, double-blind, placebo controlled study is the FIH trial of the apoE-mimetic peptide CN-105. In this trial, we have demonstrated the safety and favorable PK profile of IV CN-105 in healthy adult volunteers. We found that the CL and half-life of CN-105 were relatively consistent across doses within and between subjects, and that the pharmacokinetic data of CN-105 administered as single IV doses between 0.01 and 1.0 mg/kg are consistent with linearity. Furthermore, a dose proportionality analysis of the linear regression of the log area under the plasma drug concentration-time curve versus the log total dose suggests that the doses were proportional to various concentrations, hence CN-105 exposure increases proportionally after a single dose. The median half-life in the terminal elimination phase of CN-105 following a single high dose (0.1, 0.3 and 1.0 mg/kg) and after the last (13th) of a repeated dosing regimen showed that half-life (3.5 hr and 3.6 hr, respectively) did not change with multiple doses.

The observed half-life of 3.6 hours at higher doses in this study was longer than predicted by animal modeling (30 minutes)[34]. This highlights the difference between human and murine pharmacokinetics and the importance of the study in determining the optimal dosing interval for human subjects. The longer half-life is of practical significance as it permits a repeated dosing regimen rather than a continuous infusion, thereby facilitating emergent administration in the clinical setting. Prior murine studies demonstrated a single weight-based bolus dose achieved adequate CNS concentrations to produce long-term functional improvement, suggesting a pharmacokinetic-pharmacodynamic dissociation that makes continuous exposure unnecessary[34]. Additionally, the half-life of CN-105 supports the pre-planned dosing paradigm of repeated intravenous administration every 6 hours for 72 hours. This dosing interval was extrapolated from cellular events that lead to peak cerebral edema and secondary neuronal injury. Of note, CN-105 shows minimal accumulation after repeated 6-hour IV doses, and steady state is achieved in the first 24 hrs. Thus, CN-105 has favorable clinical pharmacological properties including a predictable linear PK and dose proportionality and a sufficiently long half-life to permit intermittent dosing. Such intermittent dosing is also more practical within a critical care setting where a patient may be receiving multiple drugs that cannot be infused simultaneously due to diluent or drug-drug interactions.

Although apoE-mimetic peptides have demonstrated robust benefits in preclinical models of acute (traumatic) brain injury [22–33], spontaneous (nontraumatic) ICH may be the optimal initial therapeutic target for a number of strategic reasons. Epidemiologically, ICH is a deadly condition that lacks effective treatment options and carries a high rate of morbidity and mortality[1] that has not improved in the last 20 years [5]. To date, multiple surgical clinical

trials in ICH have failed to show any significant benefit [35,36], and despite further ongoing surgical trials, a paradigm shift towards alternative therapies targeting other mechanisms of neuronal injury may be necessary. ICH is a clinically devastating condition with an urgent need for an alternative therapeutic entity; this makes it an attractive initial clinical outlet for pharmacological interventions designed to reduce neuroinflammatory responses. It is logistically feasible because patients present acutely and are cared for in the controlled environment of a neurointensive care or step-down unit [6]. Unlike TBI, patients are more likely to be accompanied by a legally authorized representative, facilitating recruitment. As opposed to ischemic stroke, in which a core area of brain tissue may undergo early irreversible injury, secondary neuronal injury, such as progressive cerebral edema and mass effect, following ICH tends to occur over a more protracted period raising the possibility of a prolonged therapeutic window [10]. Furthermore, clinically relevant radiographic surrogates (brain computed tomography) are readily available and standardized to accurately localize and quantify hematoma size and to characterize the evolution of perihematomal cytotoxic edema and the resultant mass effect [37]. These radiographic measures of mass effect and serum biochemical markers of glial activation, neuronal injury and neuroinflammation serve as important objective measures to capture target engagement in the initial trials of CN-105 in patients with ICH. Phase 2 trial design for ICH is also facilitated by the availability of clinically validated prognostic scoring systems based on hemorrhage size [38], location, neurological exam, and patient characteristics [39]. These considerations are particularly important given the absence of any previous successful studies in this area.

CONCLUSION

CN-105 is the leading candidate in the class of apoE-mimetic peptides derived from the receptor-binding region with the potential to improve outcomes in ICH patients when compared to the current standard of care. This Phase 1 FIH study demonstrated a linear and predictable pharmacokinetic profile. Likewise, the safety profile was reassuring, demonstrating only mild, transient adverse effects. Taken together, this favorable PK and safety profile, the wealth of preclinical data demonstrating a histologically and functionally therapeutic benefit across different models of acute brain injury, and the current clinical need for better therapeutic options for ICH patients support further development of CN-105 for treatment of this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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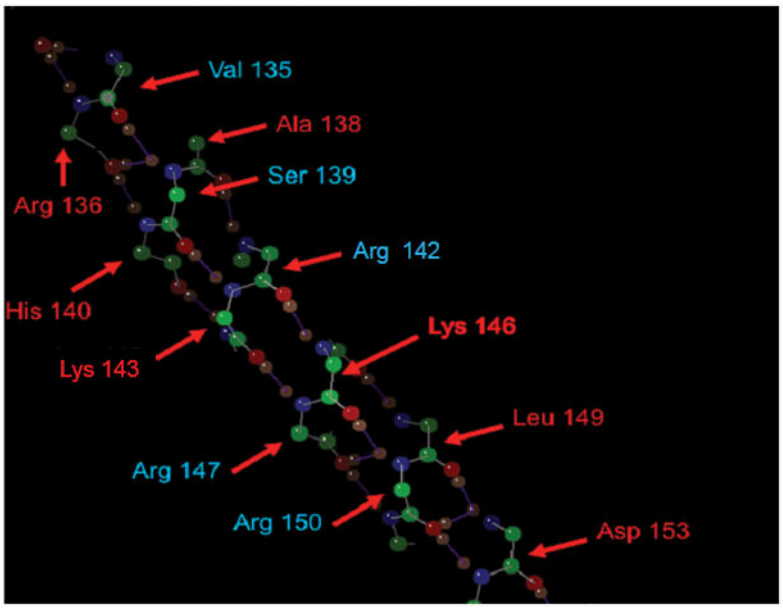

Figure 1.

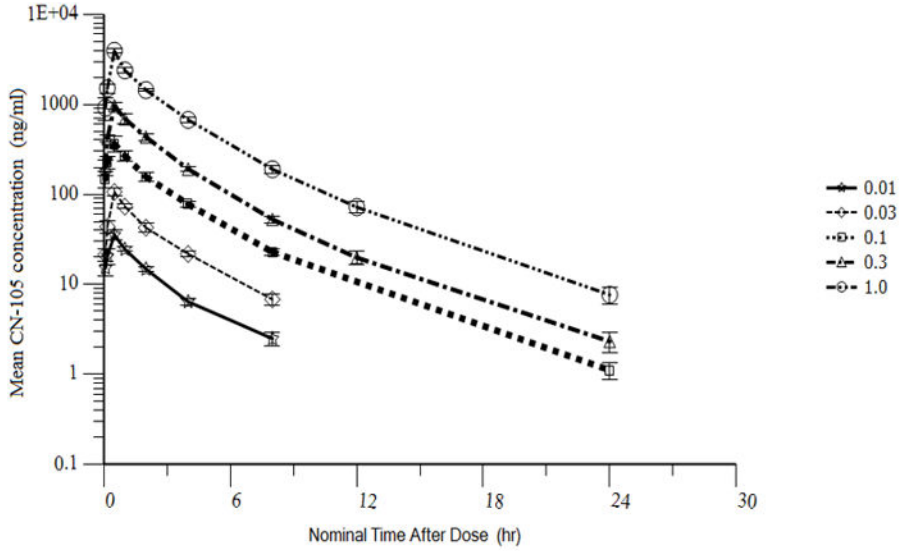

Figure 2.

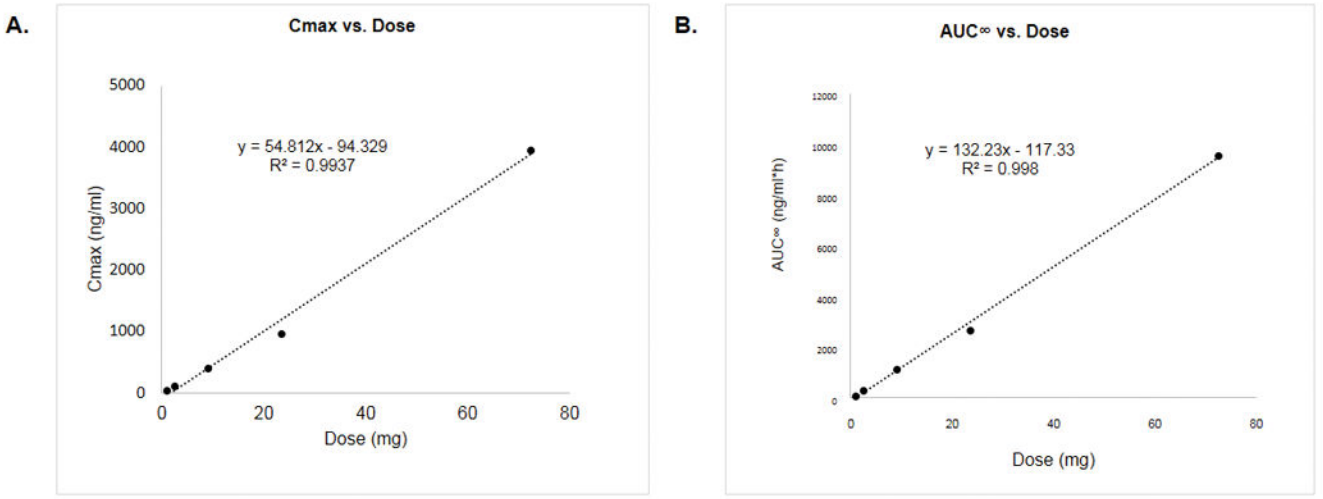

Figure 3.

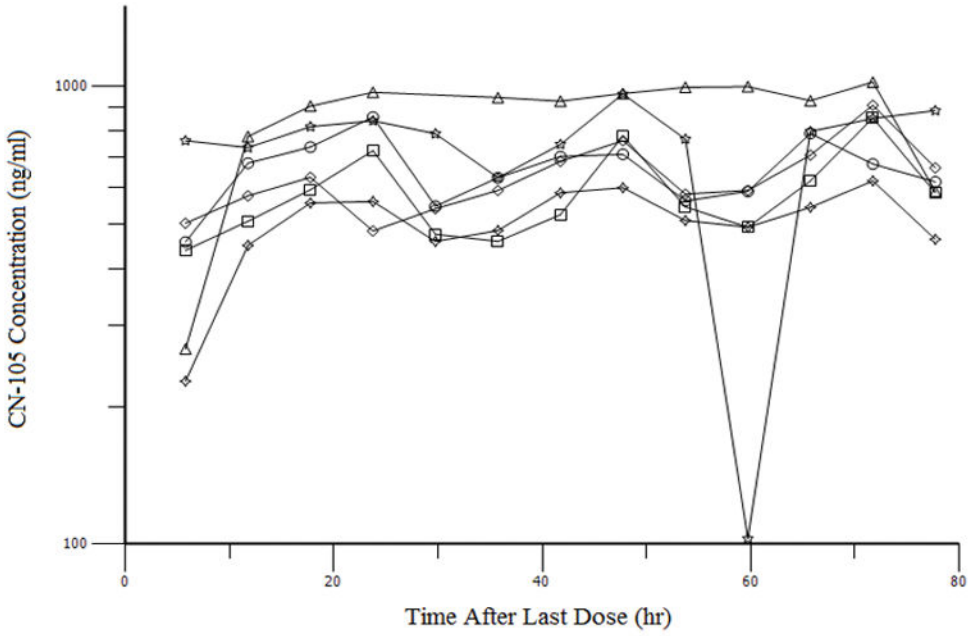

Figure 4.

Table 1

Characteristics of Enrolled Subjects

	Placebo (N=12)	CN-105 (N=36)	Total (N=48)
Age (Median) (Q1, Q3)	32.0 (28.9, 41.0)	32.4 (28.3, 37.2)	32.4 (28.3, 37.6)
Sex			
Male	9	29	38
Female	3	7	10
Race			
Black or African American	7	26	33
Caucasian	3	7	10
Other	2	3	5
BMI (Median) (Q1, Q3)	27.6 (25.1, 30.7)	26.3 (24.0, 28.4)	26.6 (24.0, 29.2)

N, number; Q, quartile; BMI, body mass index

Table 2

Pharmacokinetic values for single dose CN-105

Parameter[a]	Dose				
	0.01 mg/kg	**0.03 mg/kg**	**0.1 mg/kg**	**0.3 mg/kg**	**1.0 mg/kg**
Cmax (ng/ml)	35.7 ± 10.9	107.5 ± 25.5	407.8 ± 128.9	965.8 ± 209.3	3943.3 ± 507.0
$AUC_{0-\infty}$ (ng/ml*hr)	95.9 ±20.2	280.8 ± 39.6	1126.1 ± 194.5	2672.3 ± 272.3	9548 ± 1281.2
Volume (L)	29.8 ± 3.2	30.4 ± 8.0	38.9 ± 12.0	45.6 ± 11.2	38.4 ± 8.1
Clearance (L/h)	9.0 ± 1.1	9.0 ± 1.1	8.2 ± 1.9	8.8 ± 1.5	7.7 ± 1.7
$T_{1/2}$	2.3 ± 0.5	2.4 ± 0.5	3.3 ± 0.6	3.6 ± .4	3.5 ± 0.3

AUC $_{0-\infty}$ area under the plasma concentration–time curve from zero to infinity, *CL* clearance, *Cmax* maximum plasma drug concentration, $t_{1/2}$ half-life

[a]Data provided as mean ± SD

Table 3

Pharmacokinetic values for repeated dose CN-105 (1 mg/kg)

Dose Number	Cmax (ng/ml)	AUC_{TAU} (0–6) (ng/ml*hr)
1 (0 hr)	5011.67 (814.01)	9669.2 (1724.1)
2 (6 hr)	5340 (568.44)	10557.9 (1158.5)
13 (72 hr)	5505 (404.17)	11434.6 (1721.2)

Table 4

PK parameters for repeated doses of CN-105 administered as 1 mg/kg i.v. infusions over 30 min

Subject ID	Dose	$AUC_{TAU}1$	$AUC_{TAU}2$	Ratio 2/1	$AUC_{TAU}13$	Ratio 13/1
Mean	85	9669.2	10557.9	1.1	11434.6	1.2
Geometric Mean	84.3	9536.1	10506.5	1.1	11328.6	1.2
SD	11.9	1724.1	1158.5	0.2	1721.2	0.2
CV%	14	17.8	11		15.1	
Median	86	9911.7	10448.8	1.1	11600.4	1.3
Min	69.5	7425.1	8990.5	0.9	9382.1	0.9
Max	98.8	11431.3	12581.6	1.4	14203.2	1.5