CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA: 125495
Product: C1 esterase inhibitor
Indication: Hereditary and acquired angioedema
Sponsor: Pharming
Date Received: April 16, 2013
Reviewer: Iftekhar Mahmood, Ph. D.
RPM: Nannette Cagnagun
Through: Basil Golding, M.D.

TABLE OF CONTENTS

INTRODUCTION

Attacks of localized swelling in patients with hereditary and acquired angioedema, who have a functional deficiency of the plasma protein C1INH, are discomforting and sometimes life-threatening. Intravenous administration of plasma-derived C1INH is the preferred treatment of laryngeal and severe abdominal attacks.

C1 esterase inhibitor (C1INH) is a normal constituent of human blood and is one of the serine protease inhibitors (serpins). The applicant 'Pharming Inc' is proposing a recombinant C1INH for the management of C1INH deficiency. The product is purified from the milk of transgenic rabbits, and supplied as a sterile, preservative-free, white/off-white lyophilized powder for reconstitution for injection. One IU of rhC1INH activity is defined as the equivalent of C1 esterase inhibiting activity present in 1 mL of pooled normal plasma.

1

The product is a soluble, single-chain glycoprotein containing 478 amino acids, with a molecular mass of 68 kDa, of which approximately 22% comprises oligosaccharide structures. The primary and secondary structures of the molecule and target protease selectivity are consistent with those of plasma-derived C1 esterase inhibitor.

Each vial of the product contains 2100 IU of rhC1INH, 937 mg of sucrose, 83.3 mg of sodium citrate dihydrate and 1.0 mg of citric acid monohydrate. The product does not contain preservatives and each vial is for single use only.

There are three exploratory PK studies (C1 1207, C1 1202-01, C1 1203-01) in the submission. These studies were not formally reviewed because the PK results are similar to the PK study #2 (reviewed).

C1 1304-01 OLE (the applicant stated that one of the objectives of this study was to assess PK but no PK study report was submitted in this study).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
C1 esterase inhibitor (C1INH) is a normal constituent of human blood and is one of the serine protease inhibitors (serpins). The primary function of C1INH is to regulate the activation of the complement and contact system pathways. Regulation of these systems is performed through the formation of complexes between the protease and the inhibitor, resulting in inactivation of both and consumption of the C1INH.

~~C1INH is the only known inhibitor of activated subcomponents C1s (C1 esterase) and C1r of complement component 1 (C1) of the classical pathway of the complement system.~~ C1INH exerts ~~an~~ its inhibitory effect on several proteases (target proteases) of the contact and complement systems. The effect of RUCONEST on the following target proteases was assessed *in vitro*: activated C1s, kallikrein, factor XIIa and factor XIa. Inhibition kinetics were found to be comparable with those observed for plasma-derived human C1INH.

HAE patients have low levels of endogenous or functional C1INH. Although the events that induce attacks of angioedema in HAE patients are not well defined, it is thought that contact system activation, and resulting increased vascular permeability lead to the clinical manifestation of HAE attacks. Suppression of contact system activation by C1INH through the inactivation of plasma kallikrein and factor XIIa is thought to modulate vascular permeability by preventing the generation of bradykinin.[5]

Administration of RUCONEST increases plasma levels of functional C1INH activity.

12.2 Pharmacodynamics
The complement component (protein) C4 is a substrate for activated C1s. Patients with HAE have low levels of C4 in the circulation. Like endogenous C1INH, RUCONEST shows a dose-dependent restoration of complement homeostasis of C4 in HAE patients. A dose of 50 IU/kg of RUCONEST increases plasma C1INH activity levels to greater than 0.7 IU/mL (the lower limit of normal) in HAE patients.

12.3 Pharmacokinetics
The pharmacokinetics of RUCONEST was evaluated in a Phase 1 study of 12 asymptomatic HAE patients (dose ranged from 6.25 IU/kg to 100 IU/kg). ~~The kinetics of functional C1INH were determined using a one-compartment model with a constant endogenous infusion rate to describe endogenous levels. The average empirical Bayes estimates indicated that clearance estimates decreased and half-life estimates increased with increasing dose, suggesting non-linear kinetics and a saturable elimination mechanism. A one-compartment model with Michaelis-Menten elimination was applied, which provided dose-independent estimates of Vmax (about 45 IU/min), Km (about 0.6 IU/mL), volume of distribution (about 3 L) and the endogenous infusion rate (about 12 U/min).~~ Following administration of RUCONEST (50 IU/kg) to asymptomatic HAE patients (Table 4), the mean C_{max} was 1.36 IU/mL, and the elimination half-life was approximately ~~1.5 hours~~ 2.5 hours. RUCONEST is cleared from the circulation via receptor-mediated endocytosis followed by hydrolysis/degradation in the liver. The clearance of RUCONEST was nonlinear (clearance decreased with increasing dose) over the dose range of 6.25-100 IU/kg.

Applicant: The PK parameters in Table 4 were obtained from non-compartmental analysis. The PK of 100 IU/kg was shown to demonstrate the non-linearity between these two doses in anticipation that some patients may require higher doses than 50 IU/kg.

Table 1: Baseline corrected pharmacokinetic parameters (Mean ± SD) following administration of 50 IU/kg and 100 IU/kg RUCONEST to asymptomatic HAE patients

Parameters	50 IU/kg	100 IU/kg
$C_{baseline}$ (IU/mL)	0.17 ± 0.12	**?**
C_{max} (IU/mL)	1.2 ± 0.2	**2.3** ± 0.2
T_{max} (minutes)	19 ± 6	**19** ± 6
AUC (IUxhr/mL)	3.3 ± 0.9	**10.6** ± 2.5
CL (mL/minute)	19.4 ± 7.2	**12.3** ± 2.4
Half life (hours)	2.4 ± 1.2	**2.7** ± 0.3
V_{ss}	3.1 ± 0.9	**2.4** ± 0.5

Based on Functional C1INH

~~**Table 2: Mean pharmacokinetic parameters following administration of RUCONEST 50 IU/kg to asymptomatic HAE patients**~~

~~Parameter~~	~~Mean value ± SD (N=6)~~
~~C_{max} (IU/mL)~~	~~1.36 ± 0.306~~
~~C_{max} above baseline (IU/mL)~~	~~1.18 ± 0.234~~
~~T_{max} (minutes)~~	~~18.3 ± 5.72~~
~~AUE above baseline (IU.min/mL)~~	~~218 ± 55.6~~
~~CL (mL/minute)~~	~~22.8 ± 7.34~~
~~Half life (min)~~	~~93.7 ± 8.45~~
~~Volume (Liters)~~	~~3.03 ± 0.794~~
~~$C_{baseline}$ (IU/mL)~~	~~0.175 ± 0.116~~

~~One IU equals the mean (endogenous) C1INH content in one milliliter of plasma in healthy subjects. Functional C1INH levels are presented, representing the combined activity of endogenous C1INH and RUCONEST.~~

~~$C_{baseline}$: concentration at baseline; CL: clearance; C_{max}: maximum concentration; C1INH: complement component 1 esterase inhibitor; HAE: hereditary angioedema; kg: kilogram; L: liters; min: minute; mL: milliliter; SD: standard deviation; T_{max}: time to maximum concentration; AUE: Area Under Effect curve~~

~~A Population PK (PPK) model based on 214 administrations in 120 symptomatic and asymptomatic HAE patients and healthy volunteers, confirmed that the pharmacokinetics of RUCONEST can be best described by simple Michaelis-Menten elimination kinetics. PPK simulations using the model indicate that administration of a single dose of RUCONEST 50 IU/kg ensures that almost all HAE patients achieve plasma C1INH activity levels greater than 0.7 IU/mL, which is the lower limit of the normal range.~~

Studies have not been conducted to evaluate the PK of RUCONEST in special patient populations, identified by, race, age (pediatric or geriatric), or the presence of renal or hepatic impairment.

RECOMMENDATION

The pharmacokinetic study design and results of C1 esterase inhibitor (RUCONEST) is acceptable. The applicant should modify clinical pharmacology labeling as suggested by the FDA.

Iftekhar Mahmood, Ph. D.
Clinical Pharmacology Reviewer
Division of Hematology
Office of Blood Review & Research

Basil Golding, M. D.
Division Director, Division of Hematology
Office of Blood Review & Research

Study #1

Study Title: A phase I study of the safety, tolerability, immunogenicity and pharmacokinetics of repeated intravenous doses of recombinant human C1 inhibitor in healthy volunteers ((b)(4)0417/ Pharming C1 1106-02).

The objectives of the study were to assess the safety, tolerability, immunogenicity, and pharmacokinetics (PK) of recombinant human C1 inhibitor (rhC11NH) following repeated dosing in healthy volunteers.

This was an open label, single center, repeat-dose study in which healthy subjects received 5 doses of rhC11NH at 100 U/kg intravenously (flow rate of 6 mL/min at a fixed concentration of 141 U/mL (batch CZ069) or 144 U/mL (batch number CZ067), with a washout period of approximately 3 weeks. Twenty-one healthy subjects gave informed consent for study participation. Of this population, 5 subjects were excluded from study participation because they met exclusion criteria and 2 subjects (number (b)(4) and (b)(4)) who were eligible for participation did not participate since they were recruited as backup subjects only. Thus 14 subjects (including 2 replacements) were administered study drug at least once. This population consisted of 10 females and 4 males, who were all from Caucasian ethnic origin, except for one subject, who was from mixed (Caucasian/Asian) ethnic origin. For 12 subjects who received all 5 doses, there were 4 males and 8 females (age ranging from 19 to 40 years).

Blood samples for PK study (for functional C11NH (as well as the levels of antigenic C1INH, C1q and C4 at baseline) were collected till 24 hours. Functional C11NH (drug concentration assay) was determined as inhibitory activity towards C1s protease by using a ---(b)(4)--- assay. The levels of antigenic C11NH and C4 were determined by using validated ---(b)(4)--- assays. The levels of antigenic C1q were determined by using a validated (b)(4) method.

The pharmacokinetic parameters were estimated using both compartmental (one compartment model) and non-compartmental analysis. Compartmental analysis was done assuming both linear and non-linear (Michaelis-Menten) elimination. The results of the pharmacokinetic study are summarized below.

Table 1: PK parameters of rhC11NH in healthy subjects

| Parameters	Visit 1	Visit 3	Visit 5
Baseline (U/mL)	0.92 ± 0.12	0.94 ± 0.15	0.86 ± 0.16
C_{max} (U/mL)	3.5 ± 0.6	3.5 ± 0.4	3.3 ± 0.3
Clearance (mL/min)	11.5 ± 0.4	NR	NR

NR = not reported

The half-life and clearance and of rhC11NH based on linear model dependent PK analysis were 2.5 hours and 11.5 mL/min, respectively. The Michaelis-Menten parameters (non-linear model dependent PK analysis) V_{max} and K_m were 79 U/min and 1.20 U/mL, respectively.

The average concentration-time profile, constructed from all available data, shows that after the infusion, functional C11NH concentrations increased approximately 3-to 4-fold and declined to baseline concentrations over 12 hours (Figure 1).

Conclusions: In healthy subjects, the half-life rhC11NH is short and returns to baseline values by 12 hours. Multiple dosing (every 3 weeks) of rhC11NH did not accumulate. This is not surprising because half-life of rhC11NH is only 2.5 hours.

Figure 1: Mean Concentrations vs time plot of Functional C1 inhibitor (U/mL) with SD error bars
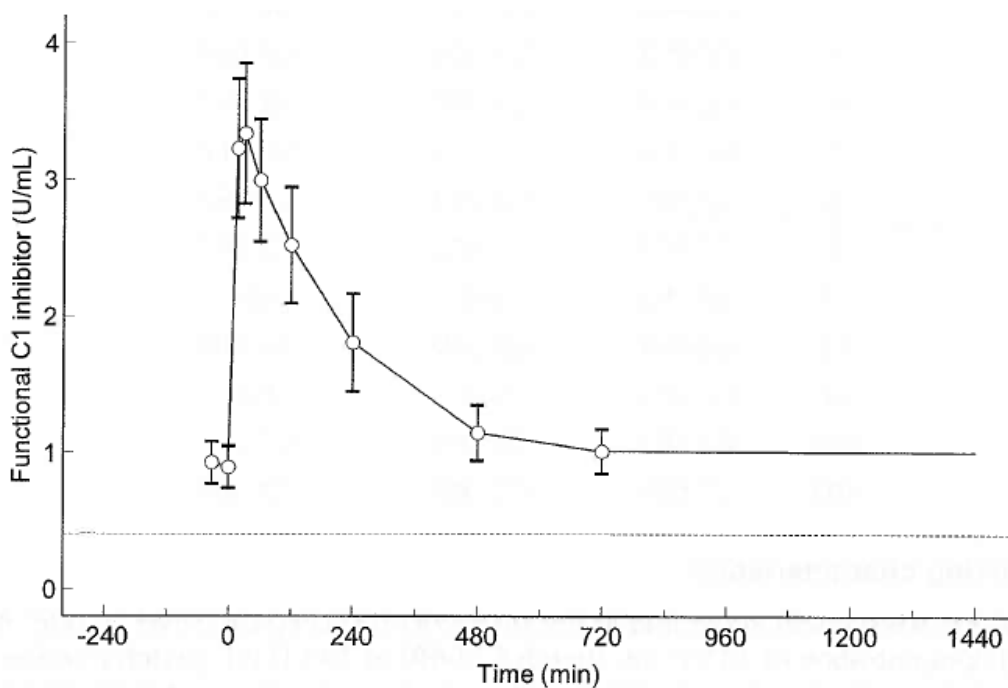
Comment

In this study, there is no evidence that rhC11NH follows non-linear pharmacokinetics.

Study Title: A Phase I exploratory study of the safety, tolerability, pharmacokinetics and pharmacodynamics of ascending intravenous doses of recombinant C1 inhibitor in asymptomatic patients with hereditary angioedema.

Twelve asymptomatic patients with HAE (type I and II), with plasma level of functional C1 inhibitor of less than 40% of normal, were included into this open label study. Screening took place at approximately 30 and / or 14 days prior to the first study drug infusion. The patients were divided into 4 groups of 3 patients and each patient was infused intravenously with recombinant human C1 inhibitor on two occasions with an interval of at least five weeks between consecutive study drug administrations. The patients stayed at the study centre for 24 hours on both infusion dates. Each patient received the dose (expressed in U/kg) as mentioned in the Table below. Overall, there were three patients each in 6.25 and 12.5 U/kg dosing groups whereas there were 6 patients each in 25, 50, and 100 U/kg dosing groups. There were 8 males and 4 females in the study (29 to 60 years of age).

	Study period (occasion) 1				Washout	Study period (occasion) 2			
Group A	6.25 (U/kg)					25.0 (U/kg)			
Group B		12.5 (U/kg)					50.0 (U/kg)		
Group C			25.0 (U/kg)					100 (U/kg)	
Group D				50.0 (U/kg)					100 (U/kg)

Schedule of administered dosages.

Blood samples for pharmacokinetic and pharmacodynamic (C4) assessment were collected at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 48, and 96 hours after drug administration. The analytical methods used were functional C1 inhibitor, antigenic C1 inhibitor, C4 assays (including C4bc). For the functional C1 inhibitor assay the --(b)(4)------- -- assay was used. For the antigenic C1 inhibitor assays, a -----(b)(4)----- method using rabbit anti-human C1 inhibitor antibodies was used (------------(b)(4)-------). For the antigenic C4 assay, a -----(b)(4)------ method using rabbit anti-human C4 antibodies was used (-----(b)(4)------).

PK/PD data analysis:

According to the applicant, the protocol stated that "The pharmacokinetic analysis will be done using compartmental and non-compartmental analysis, depending on the data obtained". Based on the actual data of functional and antigenic C1 inhibitor, it was decided to restrict compartmental PK to functional C1 inhibitor concentrations. Both non-compartmental and compartmental analysis of C1 inhibitor antigen levels was considered troublesome due to an apparent overestimation of C1 inhibitor antigen levels in the low range of detection and the

occurrence of an unexplained second peak in the profile of some of the patients. Pharmacokinetics of functional C1 inhibitor was determined using a one-compartment model with a constant endogenous infusion rate to describe endogenous levels. In addition this analysis provided empirical Bayes estimates of clearance, half-life, volume of distribution, and endogenous concentration of functional C1 inhibitor.

For compartmental analysis, calculations were performed using nonlinear mixed effect modeling (---(b)(4)---). This approach simultaneously estimates all subjects and doses assuming a common structural model but allowing subjects to be different in their parameter values.

Initial analysis with a standard one-compartment model indicated that the clearance decreased with increasing dose, indicating non-linear kinetics possibly due to a saturable elimination mechanism. A one-compartment model with Michaelis-Menten elimination was therefore also applied. This model provided empirical Bayes estimates of V_{max}, K_m, volume of distribution and endogenous infusion rate of functional C1 inhibitor.

The influence of functional C1 inhibitor on C4b/c was subsequently assessed with an indirect response PK/PD model. The model was implemented by first calculating the individual empirical Bayes estimates to describe the Michaelis-Menten pharmacokinetics of functional C1 inhibitor, and then using these parameters to describe the C4b/c profile. Since the predicted profiles did not satisfactorily capture the C4b/c response and considering the very rapid drop in C4b/c concentration, a direct response model was also tried using simple E_{max} and sigmoid E_{max} models to estimate parameters.

Non-compartmental or model independent analysis is based on concentration-time data till 12 hours because beyond this time the concentrations of C1INH reached to the baseline or near baseline values for all doses.

Results:

Model independent Pharmacokinetics of functional C1 inhibitor:

The PK parameters of C1 inhibitor by functional assay are summarized in Tables 1-2 and plasma concentrations vs time data are shown in Figure 1.

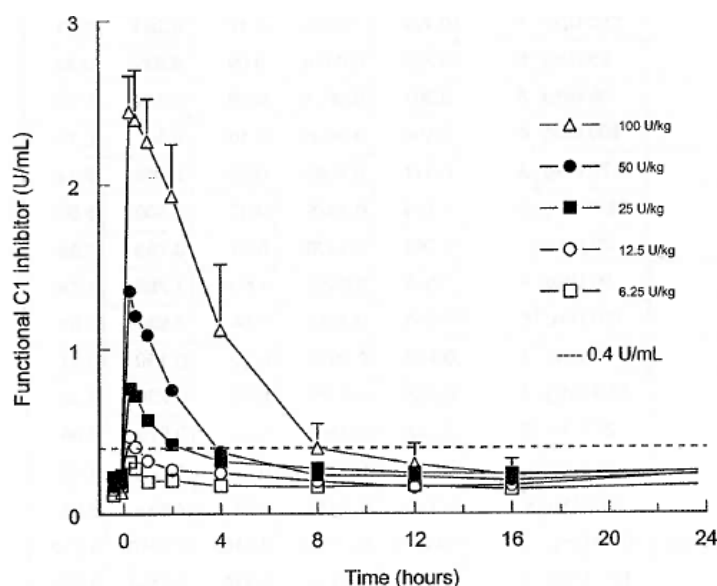**Table 1: Baseline corrected functional C1INH pharmacokinetic parameters**

Parameters	Dose (U/kg)				
	6.25	12.5	25	50	100
# of subjects	3	3	6	5	6
AUC (Uxhr/mL)	0.43 ± 0.24	0.43 ± 0.07	1.4 ±0.4	3.33 ± 1.0	10.6 ± 2.5
CL (mL/min)	24 ± 16	47 ± 9	26 ± 6	20 ±7	13 ± 2
Half-life (hrs)	3.6*	1.8 ± 1.3	2.8 ± 1.2	2.4 ± 0.6	2.7 ± 0.3
Vss (L)	4.3 ± 0.76	4.3 ± 1.1	4.3 ± 1.3	3.1 ± 865	2.4 ± 0.47

*One subject data

Table 2: Baseline uncorrected functional C1INH pharmacokinetic parameters

Parameters	Dose (U/kg)				
	6.25	12.5	25	50	100
# of subjects	3	3	6	6	6
AUC (Uxhr/mL)	2.2 ± 0.5	2.8 ± 1.4	4.1 ±1.2	5.3 ± 1.7	11.6 ± 2.7
CL (mL/min)	4 ± 1	7 ± 3	9 ± 5	12 ±2	11 ± 3
Half-life (hrs)	NA	4.7*	NA	4 ± 1	3.6 ± 0.6
Vss (L)	1.2 ± 0.2	1.9 ± 0.5	2.6 ± 1.3	2.7 ± 0.7	2.3 ± 0.47

*One subject data

Figure 1: Functional C1 inhibitor concentrations (U/mL)

Model independent Pharmacokinetics of antigenic C1 inhibitor:

The PK parameters of C1 inhibitor are summarized in Tables 3-4 and plasma concentrations vs time data are shown in Figure 2.

**Table 3: Baseline corrected antigenic C1INH pharmacokinetic parameters**

Parameters	Dose (U/kg)				
	6.25	12.5	25	50	100
# of subjects	3	3	6	6	6
AUC (µgxhr/mL)	266 ± 244	67 ± 9	394 ±170	791 ± 281	2047 ± 498
CL (mL/min)	0.04 ± 0.03	0.24 ± 0.06	0.1 ± 0.04	0.08 ±0.03	0.06 ± 0.01
Half-life (hrs)	NA	1.2*	2.7 ± 0.3	2.2 ± 0.9	3.3 ± 0.3
Vss (mL)	19 ± 11	28 ± 17	22 ± 5	16 ± 5	14 ± 3

*One subject data

Table 4: Baseline uncorrected antigenic C1INH pharmacokinetic parameters

Parameters	Dose (U/kg)				
	6.25	12.5	25	50	100
# of subjects	3	3	6	6	6
AUC (µgxhr/mL)	1270 ± 394	1231 ± 376	1686 ±467	1848 ± 456	3019 ± 545
CL (mL/min)	0.01 ± 0.0	0.01 ± 0.0	0.02 ± 0.01	0.03 ±0.01	0.04 ± 0.01
Half-life (hrs)	NA	NA	NA	NA	NA
Vss (mL)	2.3 ± 0.3	4.7 ± 0.7	7 ± 2	9.9 ± 1.4	12 ± 3

NA = Half-life could not be estimated

Figure 2: C1 inhibitor antigen concentrations (µg/mL)
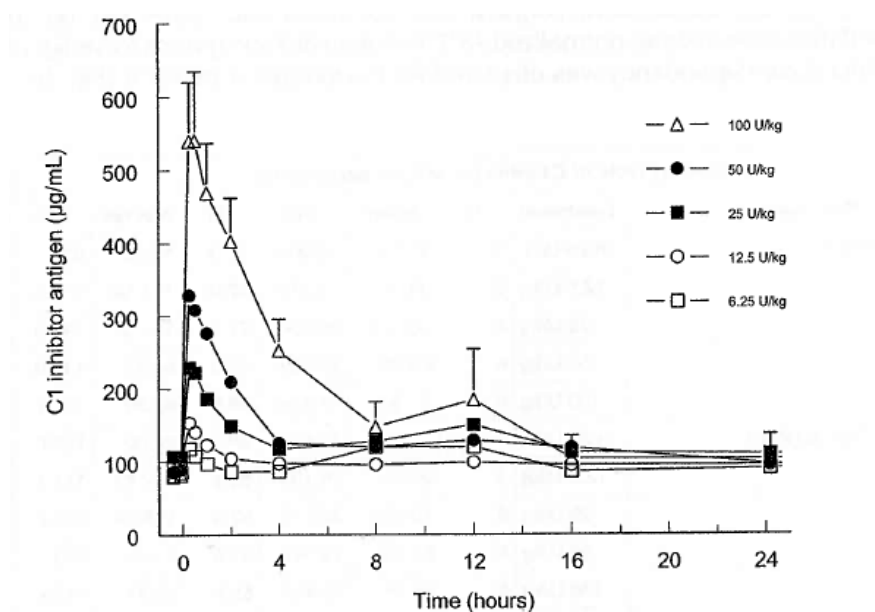
For baseline corrected PK parameters by both functional and antigenic assays, although half-life remained unchanged for doses ranging from 25 to 100 U/kg, clearance decreased at these dose levels indicating a non-linear kinetics within these doses. This phenomenon was not evident with baseline uncorrected PK parameters.

Based on the functional assay, the concentrations of C1INH were above 0.4 IU/mL (considered to be normal concentration) for 315 minutes (range:220 -719) and 550 minutes (range:525 -893) following 50 and 100 IU/kg C1INH dose, respectively.

Model Independent Pharmacodynamics of C4 antigen:

Concentrations of C4 increased with the increasing dose (dose dependent) and reached to the peak at 12 hours post-infusion (Figure 3). C4 concentrations were highly variable within the dosage groups.

Model independent Pharmacodynamics of C4b/c:

There was an immediate, dose dependent decrease in mean C4b/c concentration (normal range 100 nmol/L) (Figure 4). The duration of the C4b/c response was dose dependent. Both baseline and endogenous C4b/c levels were highly variable within and between individual subjects.
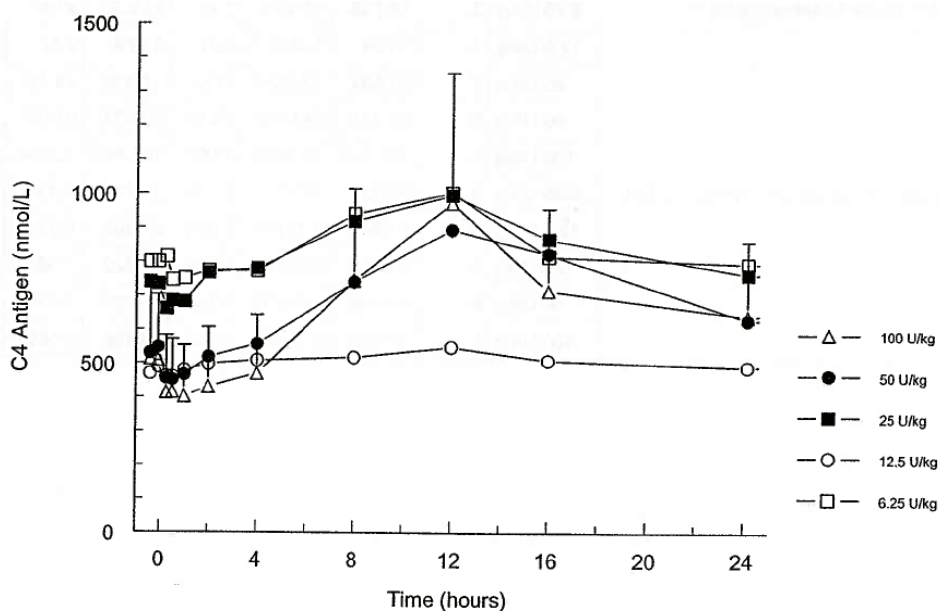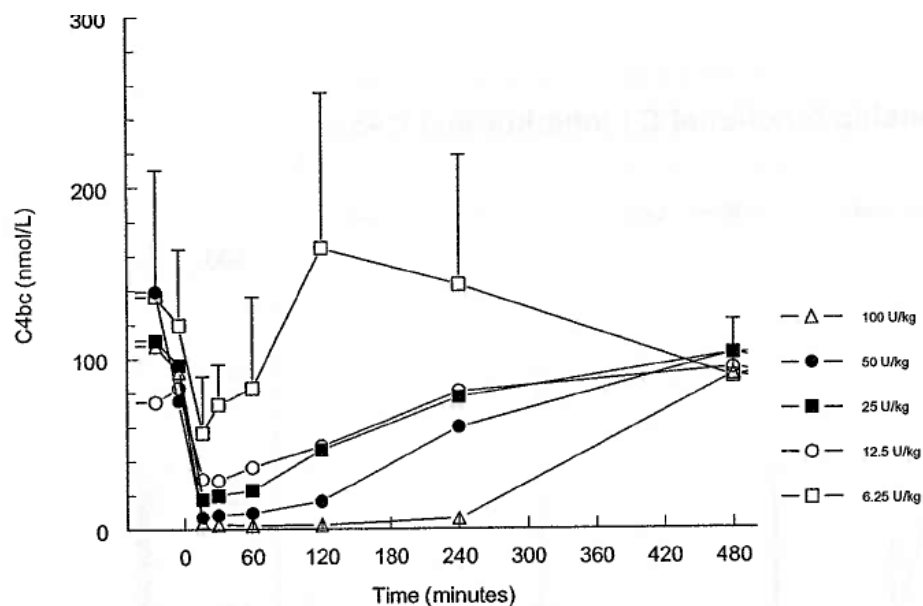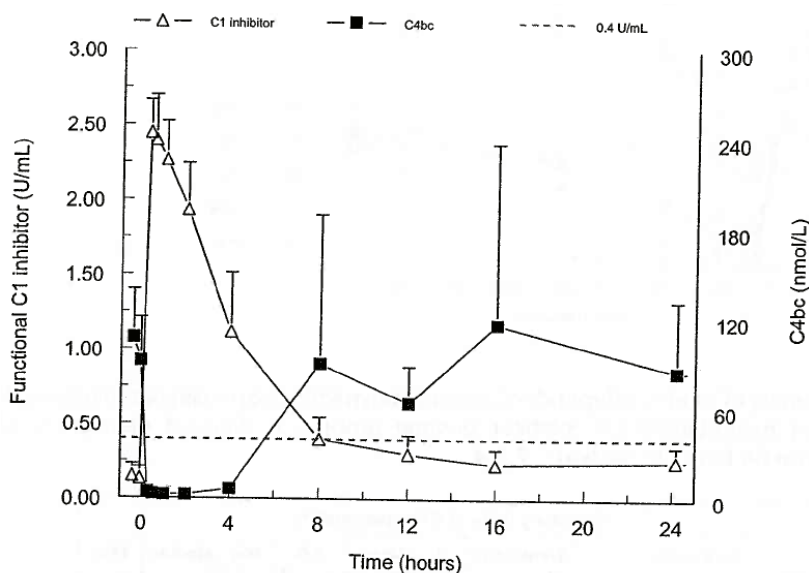
Figure 3: C4 antigen concentration (nmol/L)

Figure 4: C4b/c concentrations (nmol/L)

Relationship between functional C1 inhibitor and C4b/c levels:

Figure 5: Relationship between functional C1 inhibitor and C4b/c levels

After the infusion of rhC1 inhibitor at 100 U/kg, the C4b/c levels had dropped to values in the normal range (<8 nmol/L) and remained in the normal range for at least 4 hours. At 8 hours post-infusion C4b/c levels had returned to the high and highly variable levels observed pre-infusion.

Model dependent pharmacokinetics and pharmacodynamics:

Kinetics of functional C1 inhibitor was initially determined using a one-compartment model with a constant endogenous infusion rate to describe endogenous levels. The average empirical Bayes estimates indicated that clearance decreased and half-life increased with increasing dose, indicating non-linear kinetics suggesting a saturable elimination mechanism. The clearance of C1 inhibitor ranged from 12.7 ± 2.5 (100 U/kg dose) to 71.4 ± 10.2 (6.25 U/kg) mL/min and half-life ranged from 172 ± 36 (100 U/kg dose) to 28 ± 13 (6.25 U/kg) minutes.

Since the predicted profiles from the indirect response model did not satisfactorily capture the C4b/c response and considering the very rapid drop in C4b/c concentration, a direct response model was also tried using simple E_{max} and sigmoid E_{max} models to estimate parameters. The performance of both simple E_{max} and sigmoid E_{max} models in capturing C4b/c response was almost similar. Overall, both the indirect and direct response model failed to describe C4b/c response adequately.

Both model independent and model dependent PK analysis showed comparable pharmacokinetics of C1 inhibitor. From both analyses, non-linear kinetics at the dose range of 25-100 U/kg was evident.

Conclusions

1. After infusion of recombinant C1 inhibitor, functional and antigenic C1 inhibitor plasma C_{max} as well as the mean time of functional C1 inhibitor above 0.4 U/ml (40% of normal) increased dose dependently. With all dosages of rhC11NH a highly variable peak in C1 inhibitor antigen concentration was observed at approximately 12 hours post-infusion which was not observed for functional C1 inhibitor.

2. First-order conditional estimation (FOCE) in ----(b)(4)---- of the PK parameters of functional C1 inhibitor revealed dose dependent estimates for clearance, half-life and endogenous infusion rates, suggesting a saturable elimination of recombinant C1 inhibitor at higher doses.

3. After the infusion of C1 inhibitor at 100 U/kg, a mean clearance of 13 mL/min, a mean half-life of approximately 3 hours and a mean endogenous infusion rate of 2.2 U/min were observed (baseline corrected functional assay).

4. After infusion, mean normalized C4 levels initially decreased dose dependently. Subsequently, at approximately 4 hours post-infusion, C4 levels returned to baseline after which the levels exhibited a highly variable dose-dependent peak at approximately 12 hours post-infusion.

5. After infusion, mean C4b/c levels immediately decreased for all dosages of C1INH. The magnitude and the duration of the decrease in C4b/c levels were dose-dependent. After the infusion of C1 inhibitor at 100 U/kg, mean C4b/c levels had returned to relatively high levels at approximately 8 hours post-infusion; at that time the mean functional C1 inhibitor concentration had dropped to 0.4 U/ml.

6. In view of the individual predicted profiles, the indirect response model did not satisfactorily capture the C4b/c response. The maximum observed decrease in C4bc concentration tended to be more pronounced than predicted and stayed at a low level for a longer period of time.