

CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125325/0

Product: Alpha-1 Proteinase Inhibitor

Sponsor: Kamada, Ltd

Indication: For the treatment of patients with Alpha1-antitrypsin deficiency

Date Received: June 1, 2009

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TABLE OF CONTENTS

Introduction	1
Clinical Pharmacology Labeling Comments	2
Recommendations	4

Study #1: The pharmacokinetics and safety of an Alpha-1 proteinase inhibitor (-(b)(4)--API) in subjects with congenital API deficiencies. A dose-escalation clinical trial.	5
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INTRODUCTION

Alpha1-Proteinase Inhibitor (API) deficiency, also called Alpha1-Anti-Trypsin (AAT) deficiency, is a genetically determined disease. The deficiency of API occurs as a result of the inheritance of a pair of protease inhibitor (PI) deficiency alleles at the API genetic locus (designated as PI). The most common deficiency allele is PI*Z which is present in about 1 in 25 individuals of Northern European descent and a large majority of individuals with severe API deficiency are of the PI type ZZ (homozygous for PI*Z).

Subjects with API deficiency are at increased risk for developing chronic obstructive pulmonary disease (COPD). It is believed that this is the result of the chronic activity of elastase released by polymorphonuclear cells continually present in the lungs in low numbers. In subjects with API deficiency this elastase is not inhibited by API, resulting in chronic lung damage.

This study was conducted to obtain the pharmacokinetic information of the Investigational Product, -(b)(4)--API, to evaluate the safety of the product, and to determine the optimal dose in subjects with congenital API deficiencies.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alpha-1 protease inhibitor (A1-PI) is a protease inhibitor synthesized principally in the liver. It is found in the blood and also in the epithelial lining fluid of the lungs where it protects the lungs from damage by the enzyme neutrophil elastase, a destructive proteolytic enzyme released by neutrophils. In normal individuals, the serum concentration of A1-PI can rise considerably during inflammatory episodes as part of the acute phase reaction [1]. The molecular mass of A1-PI allows it to enter the lungs by passive diffusion from the blood [2] where it protects the lungs against proteolysis by neutrophil elastase.

A1-PI deficiency is a chronic, autosomal, co-dominant hereditary disorder in which the reduced levels of A1-PI in the blood and lungs of predisposed individuals are insufficient to oppose the proteolytic activity of neutrophil elastase [3, 4]. This can result in damage to the pulmonary alveolar structure, typically leading to progressive, severe emphysema that can become clinically apparent as early as the third or fourth decade of life. Clinically significant lung disease is more prevalent in individuals with A1-PI deficiency than in the normal population and occurs earlier in cigarette smokers than in lifelong non-smokers [2].

A large number of phenotypic variants of A1-PI deficiency exist, not all of which are associated with the clinical disease. Ninety five percent of A1-PI deficient individuals have the PiZZ variant, typically characterized by A1-PI serum levels < 35% of normal. The current standard medical practice for treatment of A1-PI deficiency in patients with emphysema is to augment the low protease inhibitor levels by intravenous infusions. Examination of broncho-alveolar lavage specimens has shown that intravenously administered exogenous A1-PI diffuses into the lungs resulting in an increase in pulmonary A1-PI levels, and an associated increase in the anti-elastase capacity of the epithelial lining fluid [5]. Individuals with endogenous levels of A1-PI below 11 μM , in general, manifest a significantly increased risk for development of emphysema above the general population background risk[6, 7]. Therefore, the maintenance of serum levels of A1-PI (antigenically measured) above 11 μM is historically thought to provide therapeutically relevant anti-neutrophil elastase protection[8]. However, the hypothesis that maintaining a serum level of antigenic A1-PI will restore protease-antiprotease balance and prevent further lung damage has never been tested in an adequately-powered, placebo-controlled, randomized clinical trial.

12.2 Pharmacodynamics

Administration of Kamada-API to patients with A1-PI deficiency augments the level of the deficient protein. Normal individuals have levels of A1-PI greater than 22 μM .

12.3 Pharmacokinetics

A prospective, open-label, uncontrolled multicenter pharmacokinetic study was conducted in 7 females and 11 males with A1-PI deficiency, ranging in age from 40 to 69 years. Subjects with congenital A1-PI deficiency received a single dose of Kamada-API either 30 mg/kg, 60 mg/kg or 120 mg/kg. Blood samples for pharmacokinetic study were taken prior to and within 5 minutes of completion of the infusion, and then at 1 hour, 6 hours, 12 hours, 24 hours, 3 days and 7 days. The mean results for pharmacokinetic parameters in the 60 mg/kg dosage group are shown in Table 1. The pharmacokinetics of A1-PI was linear over the dose range of 30-120 mg/kg.

~~The mean AUTCC to Day 7 value was 1,979 h* μ M, the mean terminal half life was 111 hours, the mean volume of distribution was 3.02 L and mean clearance was 0.62 L/day. Projected values based on antigenic assay results indicated that at Week 12 a mean trough level in excess of 11 μ M would be achieved by 76% of patients in the 60 mg/kg group.~~

Table 1 Pharmacokinetic Parameters for Antigenic A1-PI (Dosage 60 mg/kg; n=6)

Pharmacokinetic Parameter	60 mg/kg Dose Group
Terminal Half Life (hours)*	111 \pm 33
Area under the curve _(0-168 hrs) (mg*hours/mL)	89 \pm 10
Clearance (mL/hr/kg)	0.68 \pm 0.1
Volume of Distribution (L)	3.2 \pm 0.3

*Any assessment of the clinical relevance of half-life in this study should be viewed with caution.

RECOMMENDATION

The pharmacokinetic study of Alpha-1 Proteinase Inhibitor is acceptable. The sponsor should incorporate the clinical pharmacology labeling of Alpha-1 Proteinase Inhibitor as suggested by the FDA.

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Title of Study: The pharmacokinetics and safety of an Alpha-1 proteinase inhibitor (b)(4)-API in subjects with congenital API deficiencies. A dose-escalation clinical trial (Study Protocol # (b)(4)-API 001).

This was a multi-center study and the primary objective of this study was to determine the pharmacokinetics of Alpha-1 proteinase inhibitor (b)(4)-API at three different dose levels in subjects with API deficiency. The secondary objective was to evaluate the safety of (b)(4)-API.

Eighteen subjects (6 per dose group) with congenital API deficiency received a single dose of the (b)(4)-API at one of the three dose levels; 30mg/kg, 60mg/kg or 120 mg/kg. There were 11 males and 7 females in the study (age ranged from 40 to 69 years). Each subject received a single dose of (b)(4)-API at an infusion rate of 0.08mg/kg/minute. Blood samples were taken prior to and within 5 minutes of completion of the infusion, and then at 1 hour, 6 hours, 12 hours, 24 hours, 3 days and 7 days. The subjects were followed up for a further 7 days (to Day 14) for safety data. Subjects were also followed up at 4 weeks and at 3 and 6 months for viral safety data. Plasma concentrations of (b)(4)-API were determined by both antigenic and functional assay methods. Plasma concentrations vs time data were fitted to one- or two-compartment model as found suitable. For antigenic assay (nephelometry), there were 2 subjects in the 120 mg/kg dose group whose data could not be fitted to two compartment model therefore; one compartment model was used to describe the data. For functional assay, all subjects' data could be fitted to two-compartment model. Results of the study are summarized below.

Antigenic (-----(b)(4)-----) assay:

Mean area under the curve ($AUC_{(0-168h)}$ and $AUC_{(0-infinity)}$) increased proportionally with dose and was linear ($r^2 = 0.999$ and 0.996 , respectively) over the dose range of 30 to 120 mg/kg. The mean terminal half-lives vary from 81 hours (30 mg/kg group) to 111 hours (60 mg/kg group) with an overall mean at 93.4 hours. The mean volumes of distribution and clearance show similar values across the dose groups, with overall mean values of 3.18 liters and 0.59 mL/hr/kg, respectively. The mean pharmacokinetics parameters of API are summarized in Table 1.

Table 1
Mean pharmacokinetic parameters of Alpha-1 Proteinase Inhibitor (Antigenic assay)

Parameters	Dose (mg/kg)		
	30 mg/kg	60 mg/kg	120 mg/kg
$AUC_{(0-168 \text{ hours})}$ mg*hr/mL	52 ± 9	103 ± 15	212 ± 39
$AUC_{(0-infinity)}$ mg*hr/mL	70 ± 14	156 ± 26	291 ± 40
Clearance (mL/hr/kg)	0.59 ± 0.10	0.59 ± 0.09	0.58 ± 0.10
Half-life (hrs)	81 ± 19	111 ± 34	89 ± 23
Volume of distribution (L)	3.18 ± 0.55	3.02 ± 0.34	3.34 ± 1.13

Clearance was calculated from $AUC_{(0-168 \text{ hours})}$ due to more than 20% contribution of tail to total AUC ($AUC_{(0-infinity)}$)

Figure 1: Mean API concentrations (antigenic 30 mg/kg)

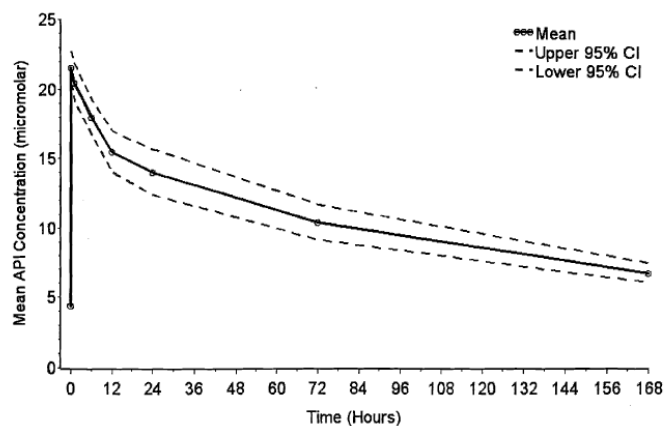


Figure 2: Mean API concentrations (antigenic 60 mg/kg)

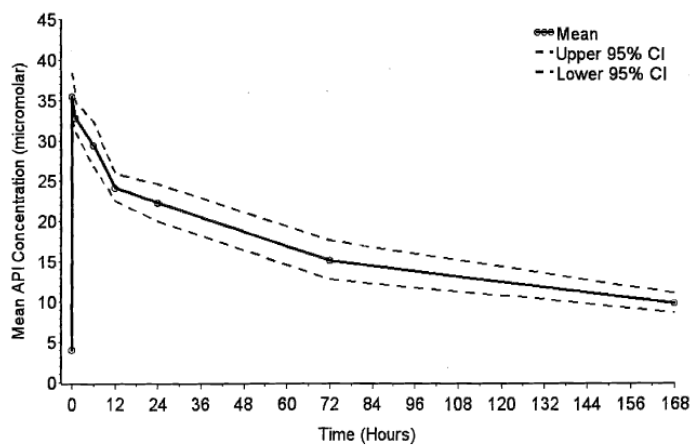
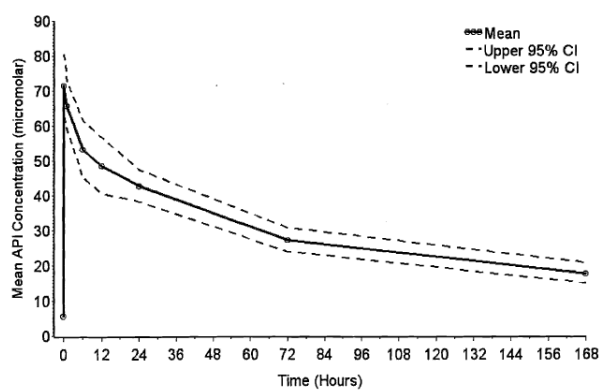


Figure 3: Mean API concentrations (antigenic 60 mg/kg)



Functional (-(b)(4)-) assay:

Mean area under the curve ($AUC_{(0-168h)}$ and $AUC_{(0-infinity)}$) increased proportionally with dose and was linear ($r^2 = 0.999$ and 0.999 , respectively) over the dose range of 30 to 120 mg/kg. The mean terminal half-lives vary from 97 hours (30 mg/kg group) to 115 hours (120 mg/kg group) with an overall mean at 107.6 hours. The mean volumes of distribution and clearance show similar values across the dose groups, with overall mean values of 3.47 liters and 0.69 mL/hr/kg, respectively. The mean pharmacokinetics parameters of API are summarized in Table 2.

Table 2**Mean pharmacokinetic parameters of Alpha-1 Proteinase Inhibitor (Functional assay)**

Parameters	Dose (mg/kg)		
	30 mg/kg	60 mg/kg	120 mg/kg
$AUC_{(0-168 \text{ hours})}$ mg*hr/mL	44 ± 8	89 ± 10	183 ± 28
$AUC_{(0-infinity)}$ mg*hr/mL	70 ± 14	156 ± 26	291 ± 40
Clearance (mL/hr/kg)	0.71 ± 0.14	0.68 ± 0.09	0.67 ± 0.10
Half-life (hrs)	97 ± 12	111 ± 33	115 ± 35
Volume of distribution (L)	3.64 ± 0.31	3.21 ± 0.31	3.57 ± 0.51

Clearance was calculated from $AUC_{(0-168 \text{ hours})}$ due to more than 20% contribution of tail to total AUC ($AUC_{(0-infinity)}$)

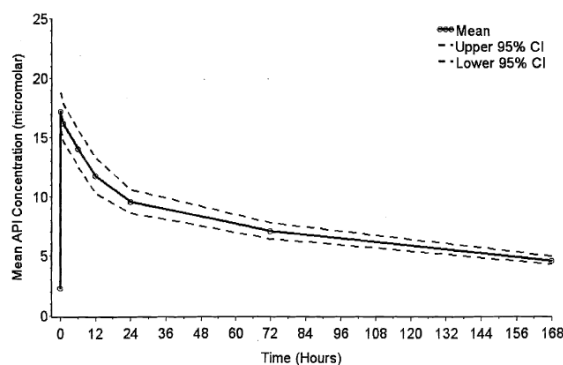
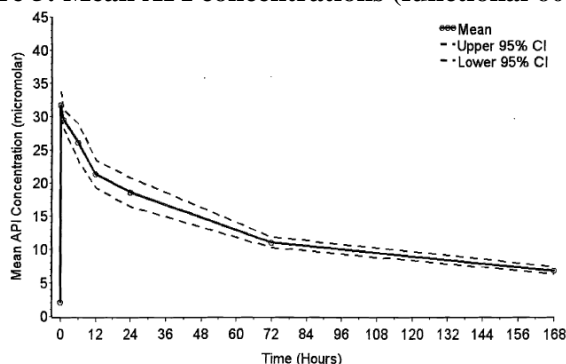
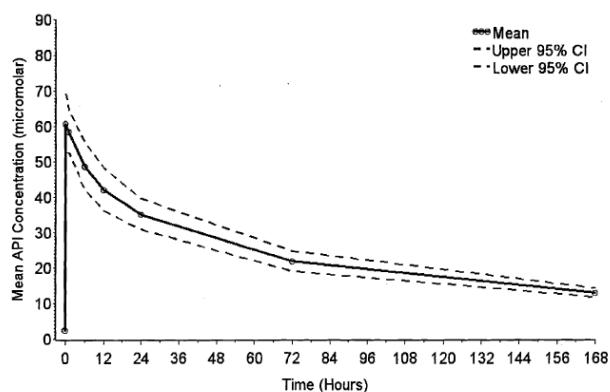
Figure 4: Mean API concentrations (functional 30 mg/kg)**Figure 5: Mean API concentrations (functional 60 mg/kg)**

Figure 6: Mean API concentrations (functional 120 mg/kg)



Conclusions

The pharmacokinetics of Alpha-1 proteinase inhibitor is linear over the dose range of 30 to 120 mg/kg. The half-life of Alpha-1 proteinase inhibitor is long but may not be of any clinical relevance because the half-life of Alpha-1 proteinase inhibitor appears to be artifact (not enough time points in the terminal phase and may be inadequate duration of blood sampling).