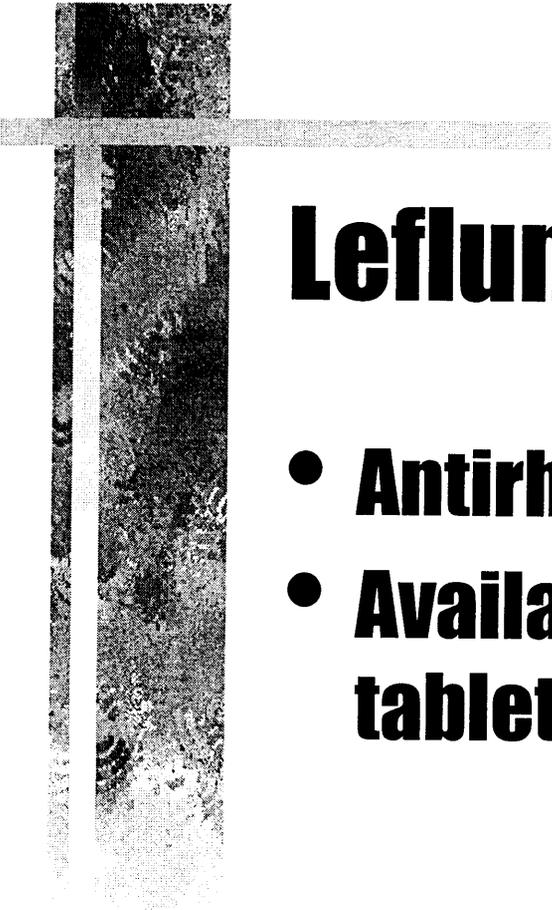


Pharmacokinetic Issues of Leflunomide

Veneeta Tandon, Ph.D.

Pharmacokinetics Reviewer

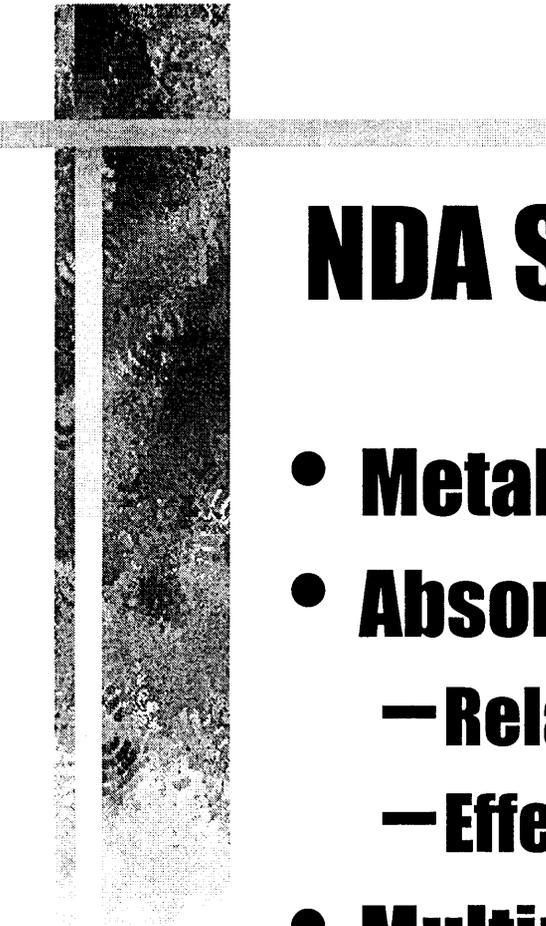
Presented at Arthritis Advisory Committee



Leflunomide

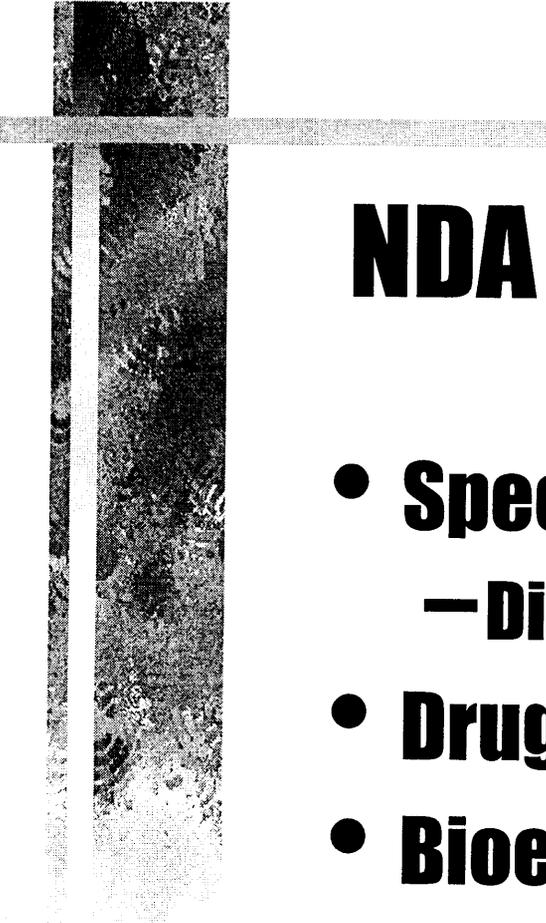
- **Antirheumatic Drug**
- **Available as 10 mg, 20 mg and 100 mg tablets**

- **# of PK studies- 23**
- **# of subjects- 632**



NDA Studies

- **Metabolism Mechanistic** **3**
- **Absorption**
 - **Relative Bioavailability** **1**
 - **Effect of food** **1**
- **Multiple Dose PK**
 - **In healthy subjects** **1**
 - **In RA patients** **6**
- **Enhancement of Elimination** **2**

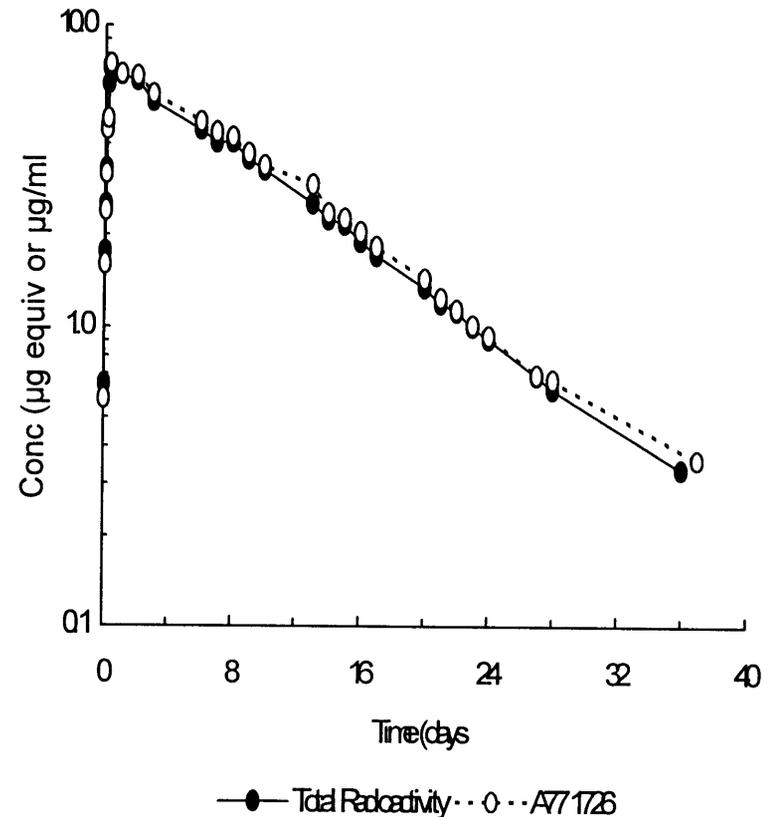


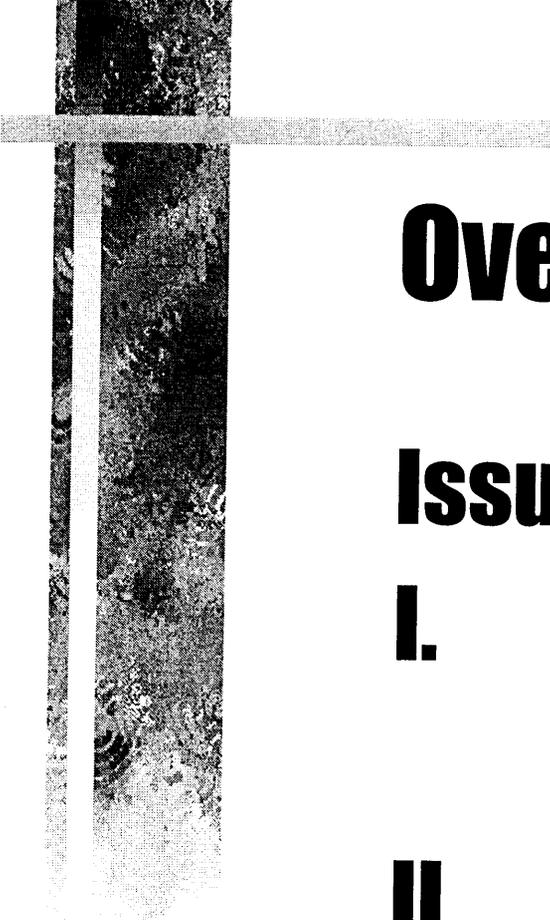
NDA Studies (con't)

- **Special Population**
 - **Dialysis patients** **1**
- **Drug interaction** **4**
- **Bioequivalence** **3**
- **Population PK**
 - **Phase I/II analysis** **1**
 - **Phase III analysis** **1**

Metabolism of Leflunomide

The pharmacokinetics of leflunomide was based on the plasma concentrations of the major active metabolite A7 1726 of leflunomide. Parent leflunomide was essentially undetectable. The total radioactivity and plasma A7 1726 levels were superimposable.





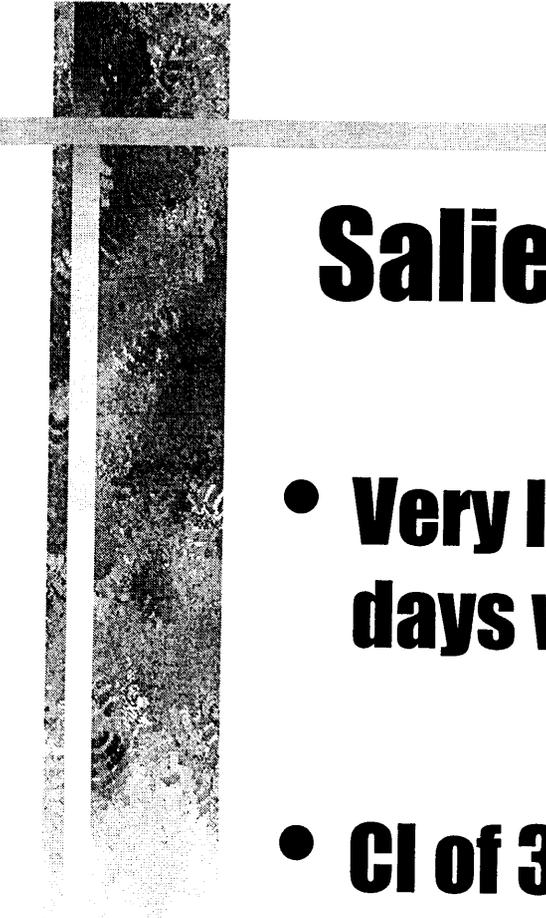
Overview

Issues:

- I. Long half-life of A77 1726**

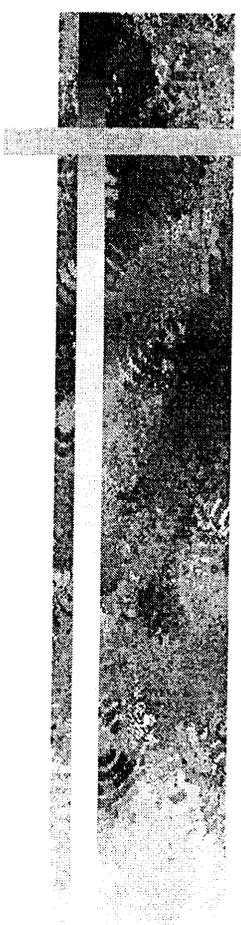
- II. Time to reach steady state**

- III. Time for elimination**



Salient Features of A77 1726

- **Very long half life ranging from 10 → 20 days with an average of ~ 15.7 days.**
- **Cl of 30 mL/h and Vss of 10 L.**
- **Poor solubility of parent drug in water (21 mg/L)**

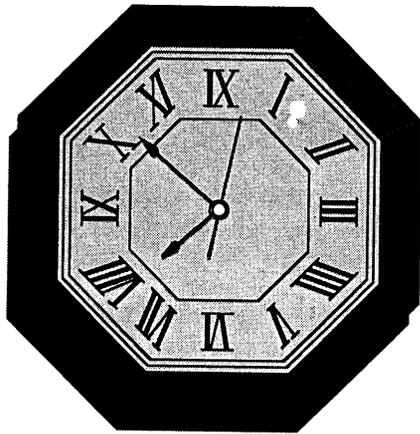


I. Half-life

Problems associated with a long half-life drug

- **Time required to reach steady state levels**
- **Time required to reach effect, i.e. Efficacy.**
- **Time required for an adverse effect to resolve.**
- **Difficulty in doing cross-over studies.**

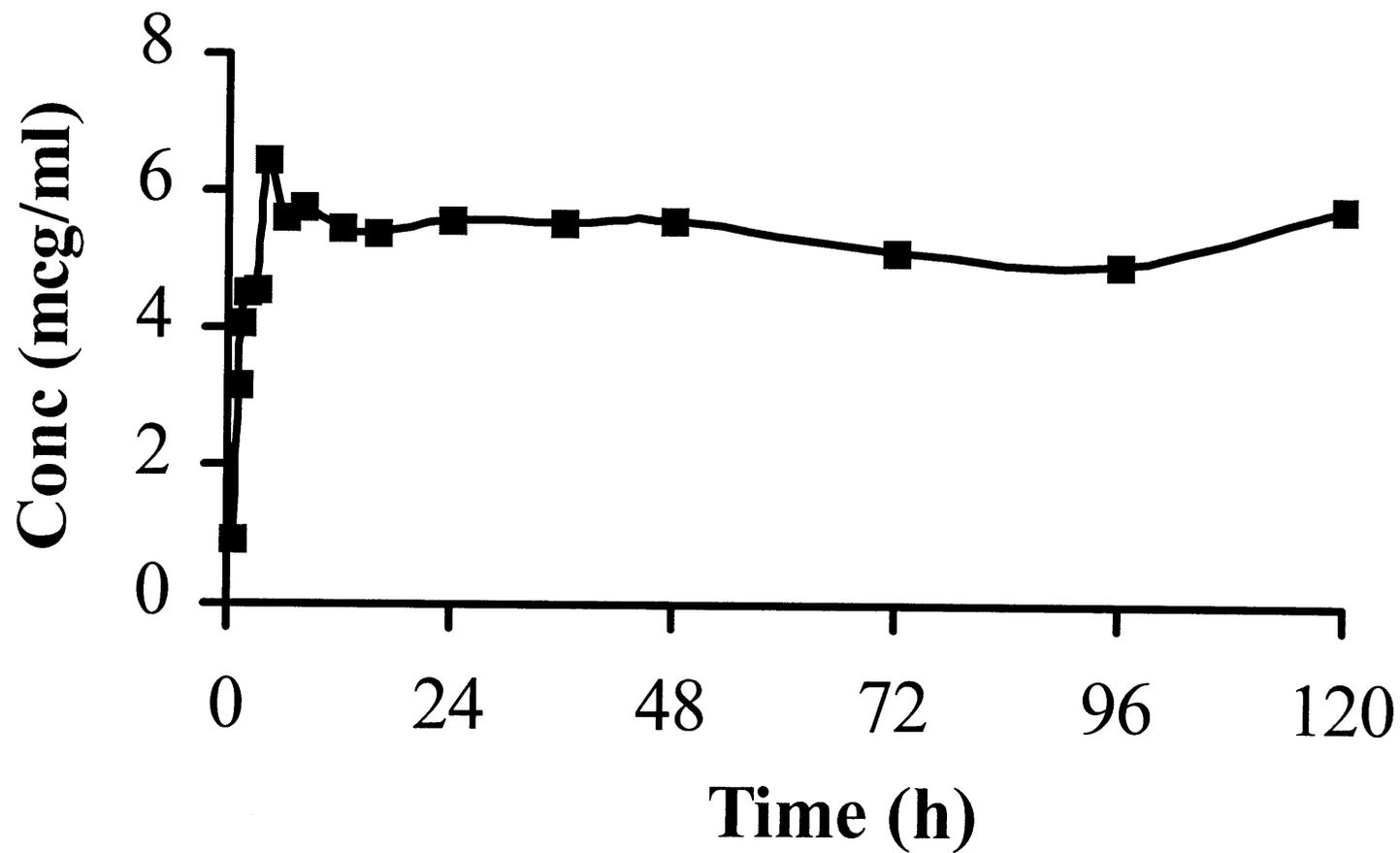
II. Time to Reach Steady State



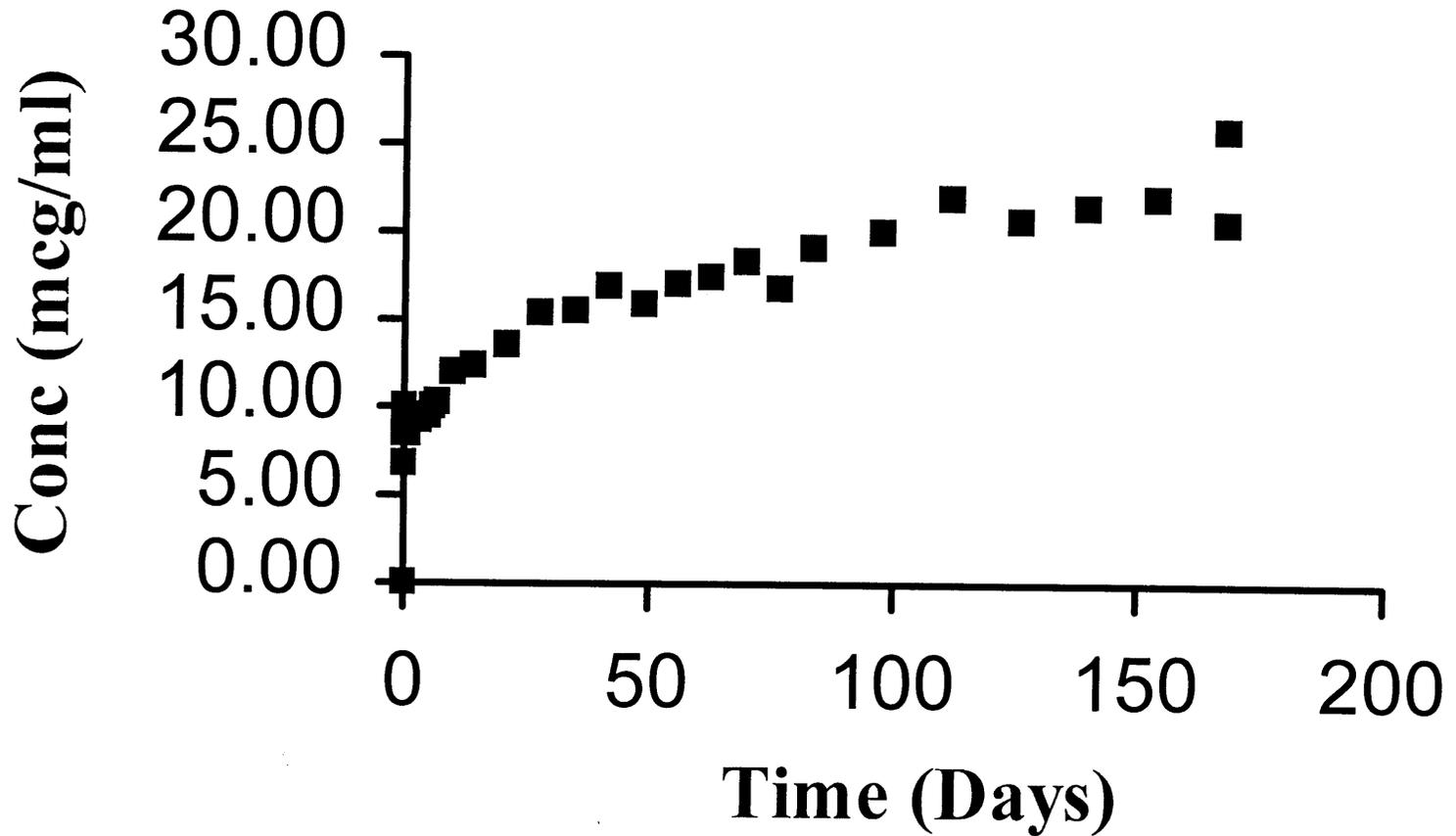
- **The time to reach steady state is $5 \times T_{1/2}$**

which is $5 \times 15.7 = 78.5$ days

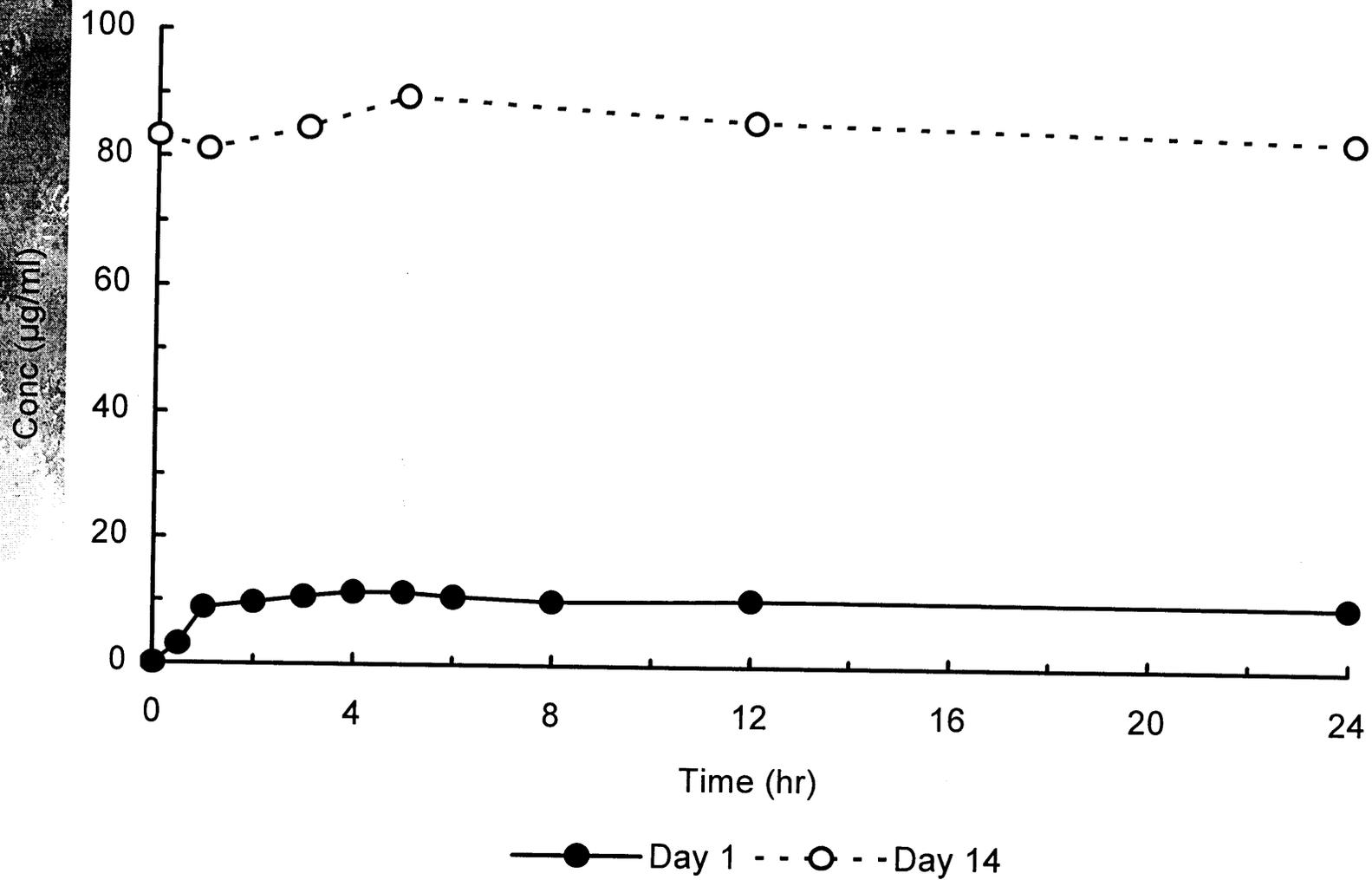
Plasma concentration profile after single dose



Plasma concentration profile after multiple dose



Observed Accumulation



Accumulation

- **Ratio of AUCs after last and first dose is 8.5**
- **Ratio of C_{\max} s after last and first dose is 7.8**

The implication of this would be the need for a loading dose to reach steady state plasma levels in a reasonable time.

Loading and Maintenance Dose Rationale in Patients

Where,

β = elimination rate constant

τ = dosing interval, i.e 24hrs.

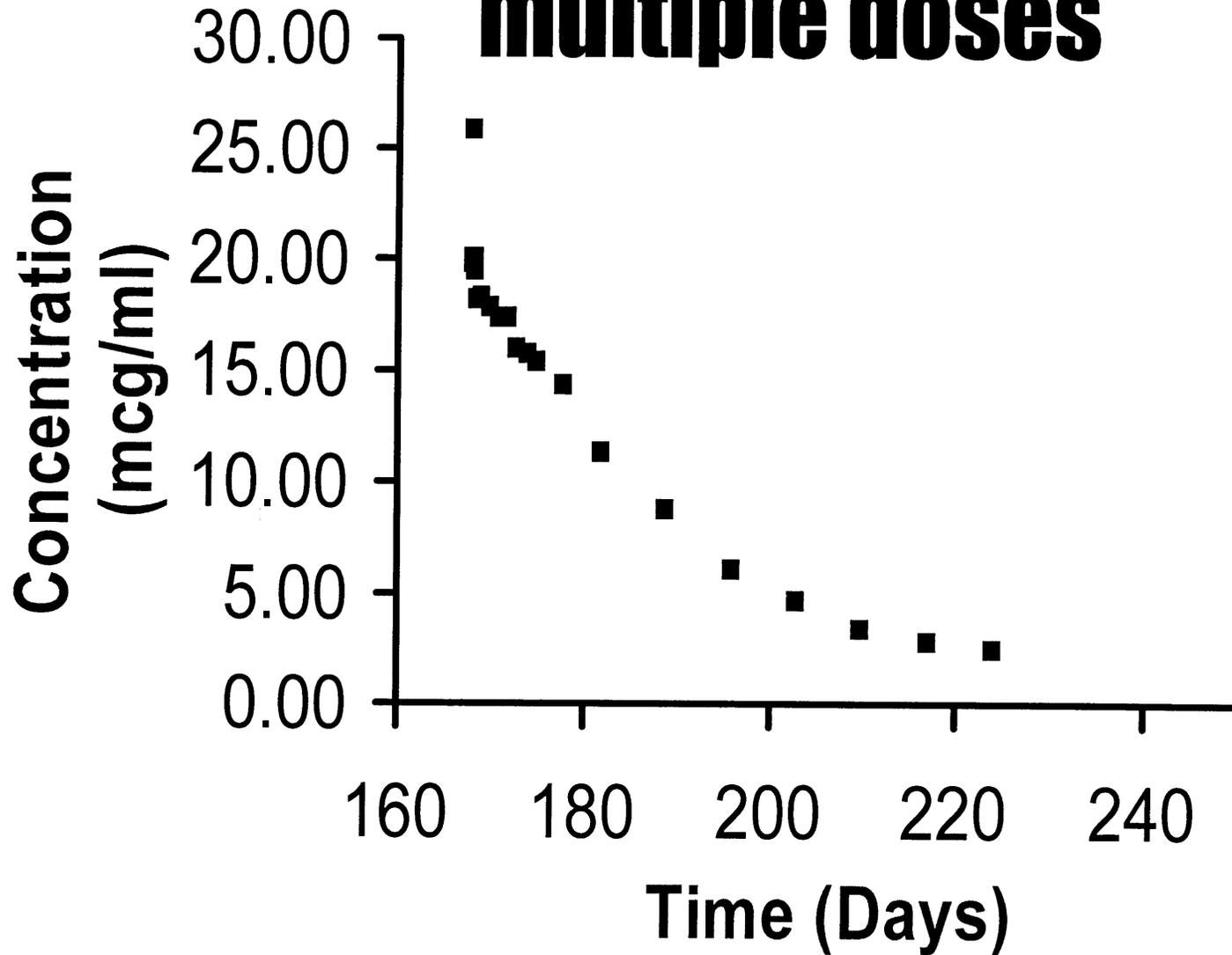
$$D_L = \frac{D_M}{1 - e^{-\beta\tau}}$$

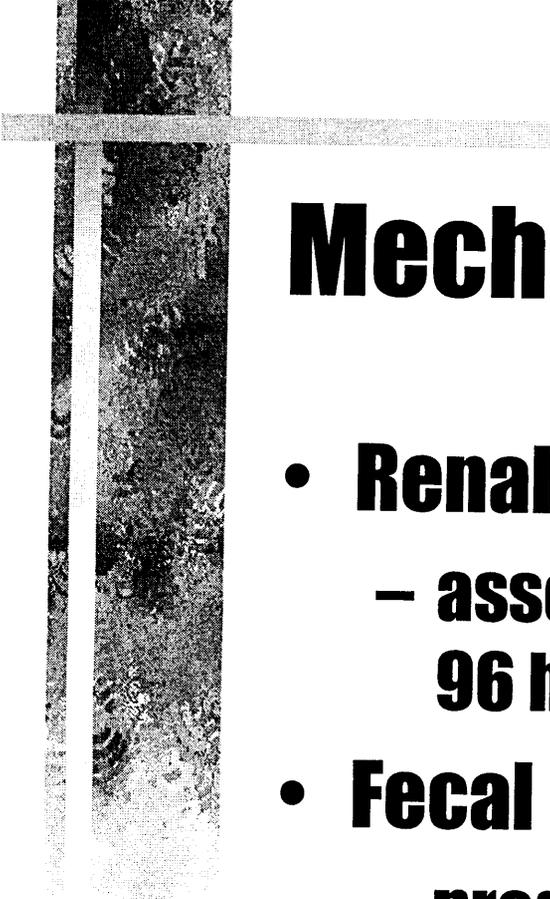
$\beta = 0.693 / T_{1/2}$

For D_M of 10 mg per day

D_L should be 230 mg.

III. Time to eliminate drug after multiple doses



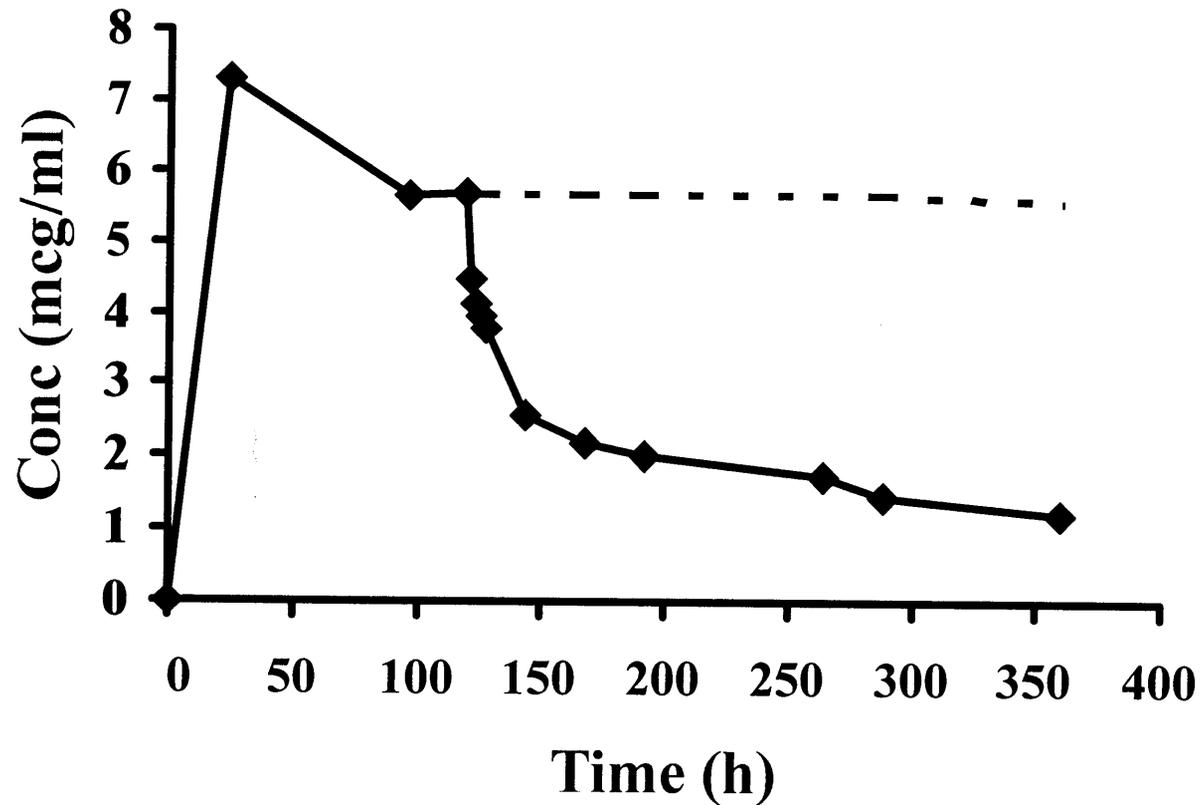


Mechanisms of Elimination

- **Renal Route**
 - **associated with drug elimination for the first 96 hours**
- **Fecal Route**
 - **predominates after 96 hours**
 - **associated with the long half-life of A77 1726**
 - **suggestive of extensive biliary elimination**

Enhancement of Elimination

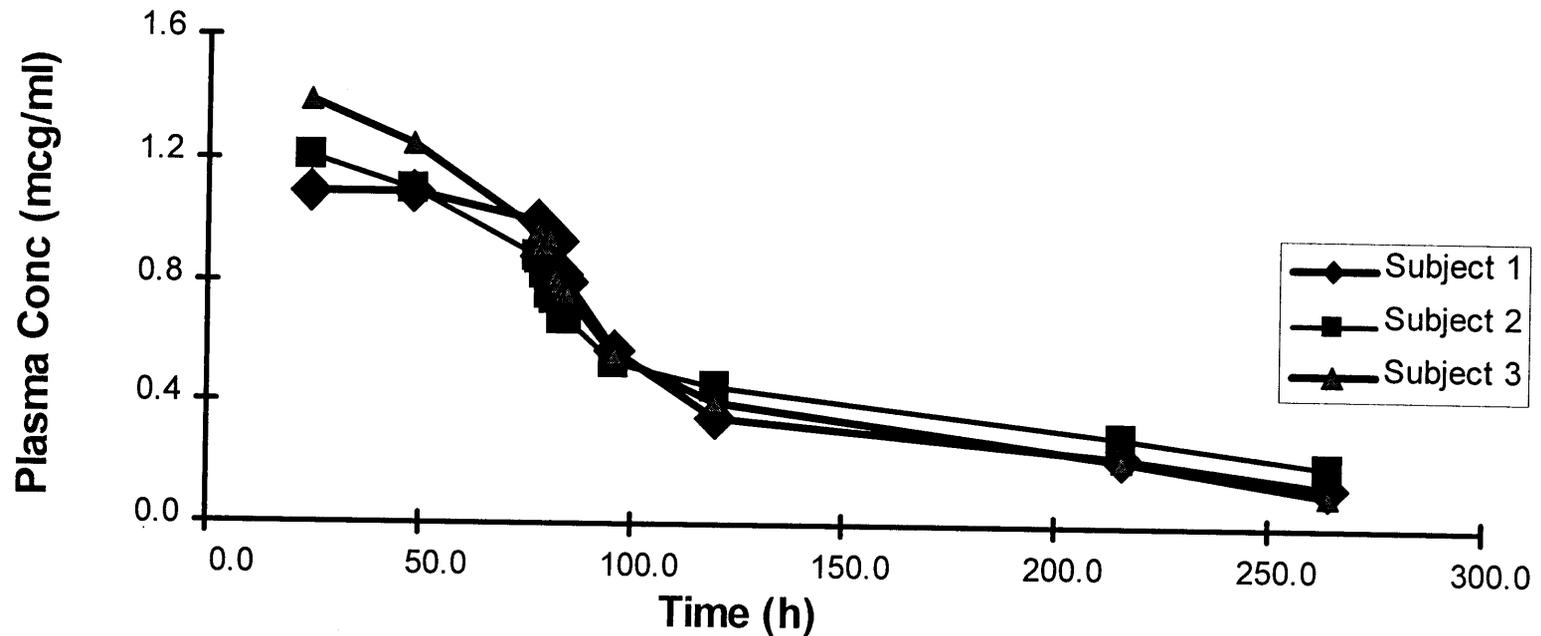
- Effect of Activated Charcoal



(3x50g charcoal given at 120,123, and 126 hrs)

Enhancement of Elimination (con't)

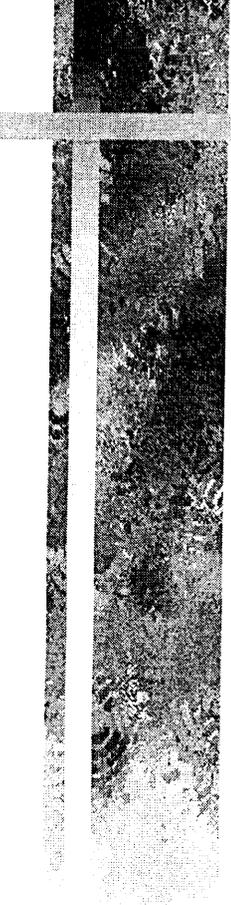
- **Effect of Cholestyramine**



(5x8g Cholestyramine given at 77.5, 83.5, 96, 215.5 and 221.5 hrs)

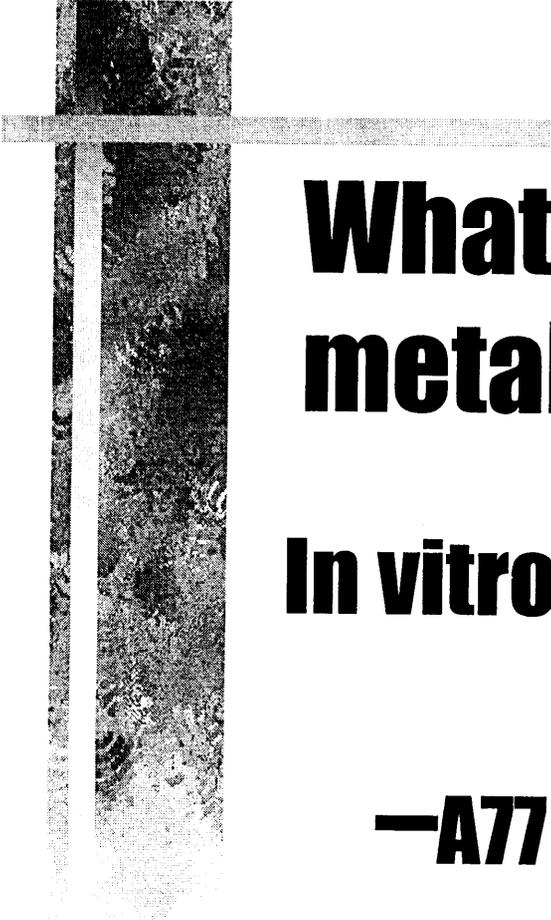
Elimination half-life before and after administration of cholestyramine

Subject	Before Cholestyramine	After Cholestyramine (3x8g)
1	417 h	25.5 h
2	115	26.3
3	99	22.9



Wrap-up

- **Long half-life**
 - **Associated with the metabolite A77 1726, leading to a high degree of accumulation.**
- **Time to reach steady state**
 - **Requires the use of a loading dose**
- **Time for elimination**
 - **Charcoal and cholestyramine can enhance elimination.**

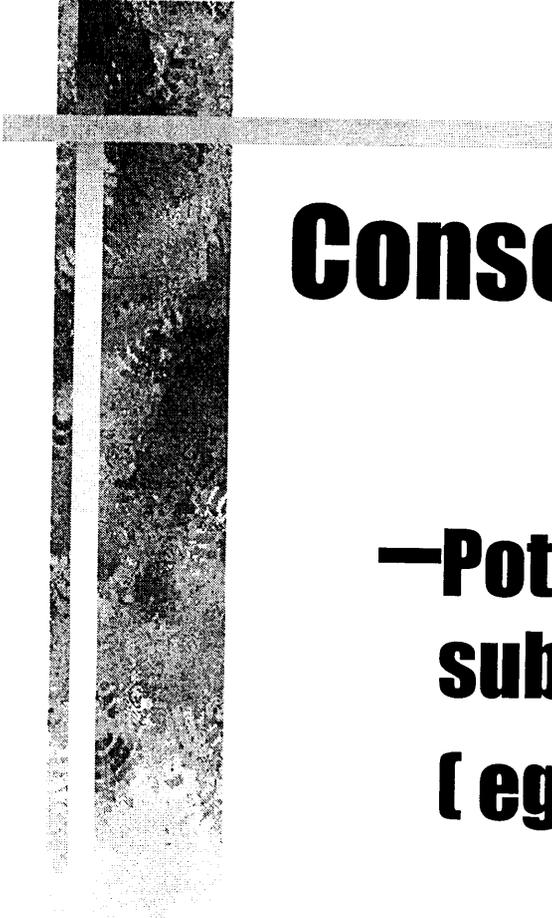


What we know from metabolism studies

In vitro metabolism

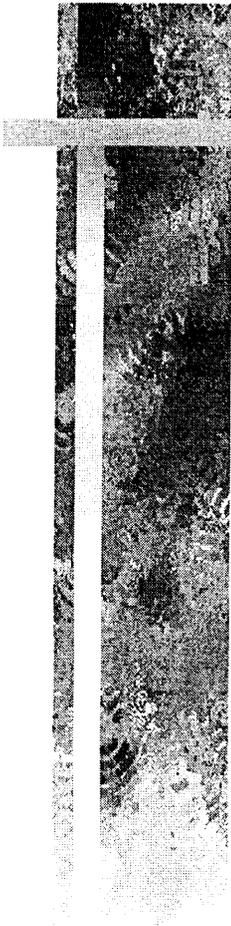
—A77 1726 inhibits CYP 2C9

**—CYP 3A4 does metabolize leflunomide to
some extent that increases with activity**



Consequence

- Potential for interaction with CYP 2C9 substrates
(eg. NSAIDS)**
- Could see an effect with both inhibitors and inducers of CYP 3A4**

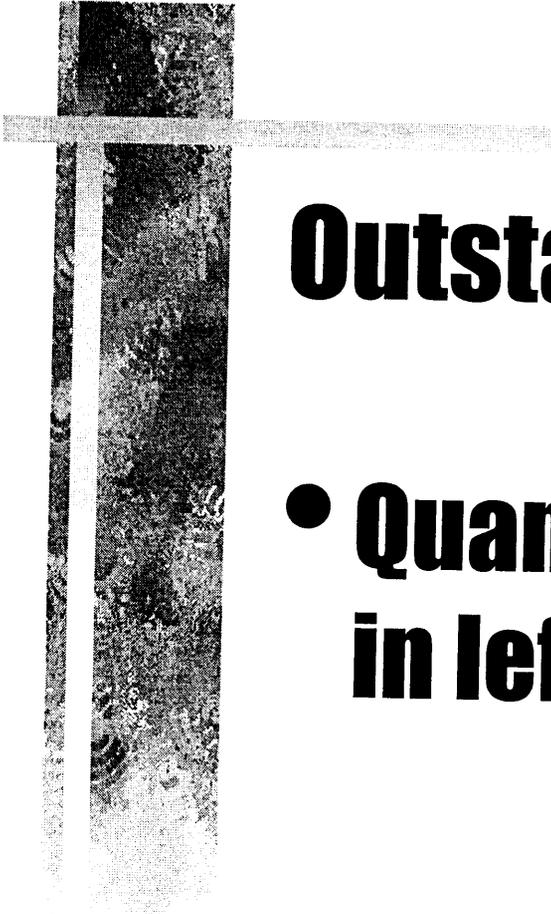


What we see in vivo

- **Rifampin causes 40% increase in C_{max}**
- **No drug interaction with Cimetidine**

From population analysis

- **No drug interaction with Diclofenac**
- **38% increase in CL of active smokers**



Outstanding Issues

- **Quantification of role of CYP 3A4 in leflunomide metabolism**
- **Follow up on Rifampin and smoking induction**