Geneva
PHARMACEUTICALS

FDA ADVISORY COMMITTEE MEETING

MARCH 13, 2003

Sanford Bolton

STUDY DESIGN FOR LEVOTHYROXINE:

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- N=24
- RELATIVELY LOW INTRASUBJECT VARIABILITY
- SINGLE DOSE CROSSOVER
- TOTAL DOSE IS 600 MCG BASED ON ASSAY CONSIDERATIONS
- MULTIPLE TABLETS OF LOWER STRENGTH
- BASELINE CORRECTION FOR ENDOGENOUS MOIETY

DOSE PROPORTIONALITY STUDY:

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1. VARIOUS STRENGTHS ARE FORMULATION DOSE PROPORTIONAL

2. PHARMACOKINETICS ARE DOSE PROPORTIONAL
50, 100 and 300 mcg tablets. Total of 600 mcg

3. DISSOLUTION IS RELATIVELY RAPID
- ALMOST 100% IN 30 MINUTES FOR ALARA AND SYNTHROID

4. THIS IS AN UNCOMPLICATED FORMULATION AND DRUG WITH REGARD TO ABSORPTION AND DISSOLUTION

DOSE PROPORTIONALITY STUDY:

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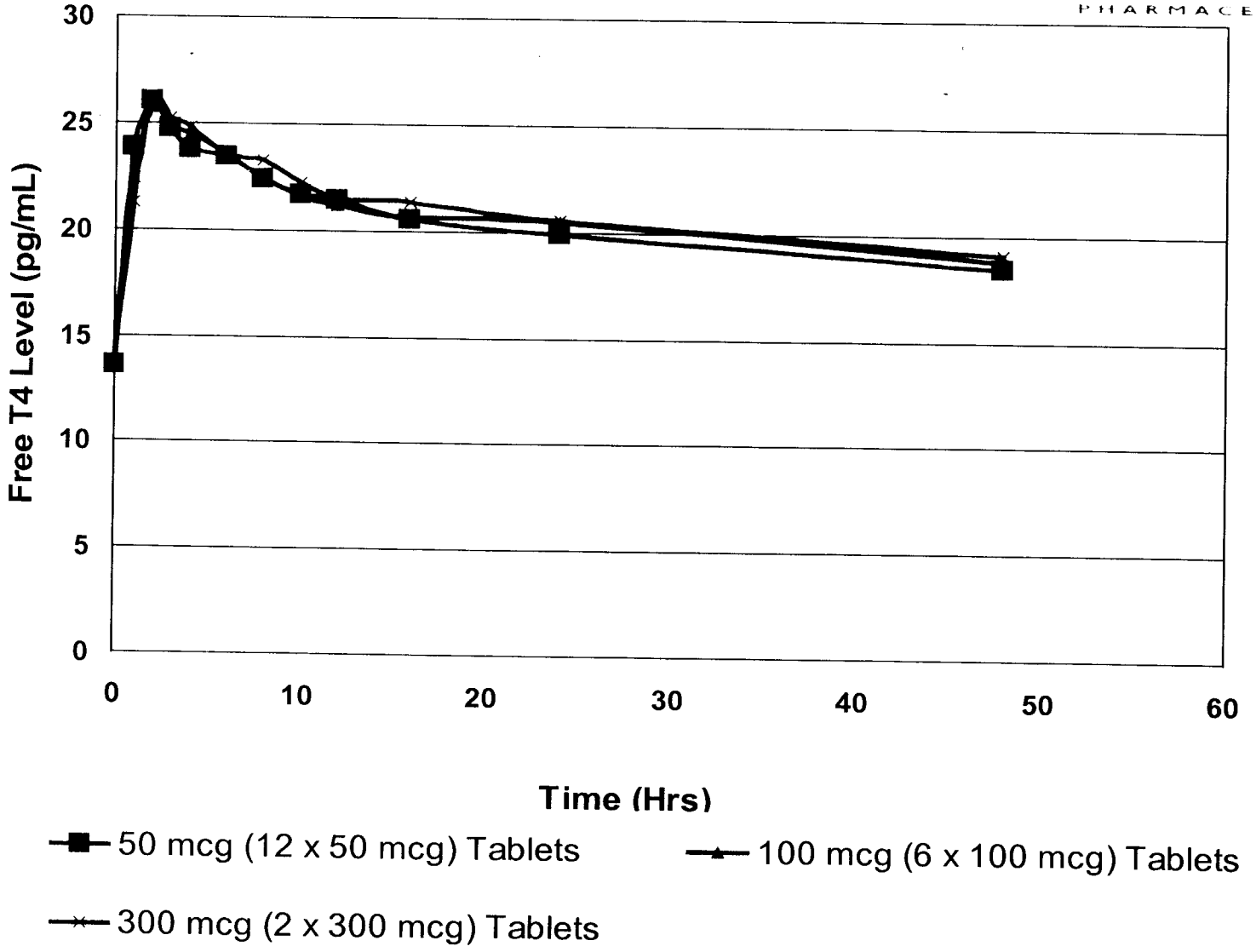

RESULTS OF BIOEQUIVALENCE STUDIES:

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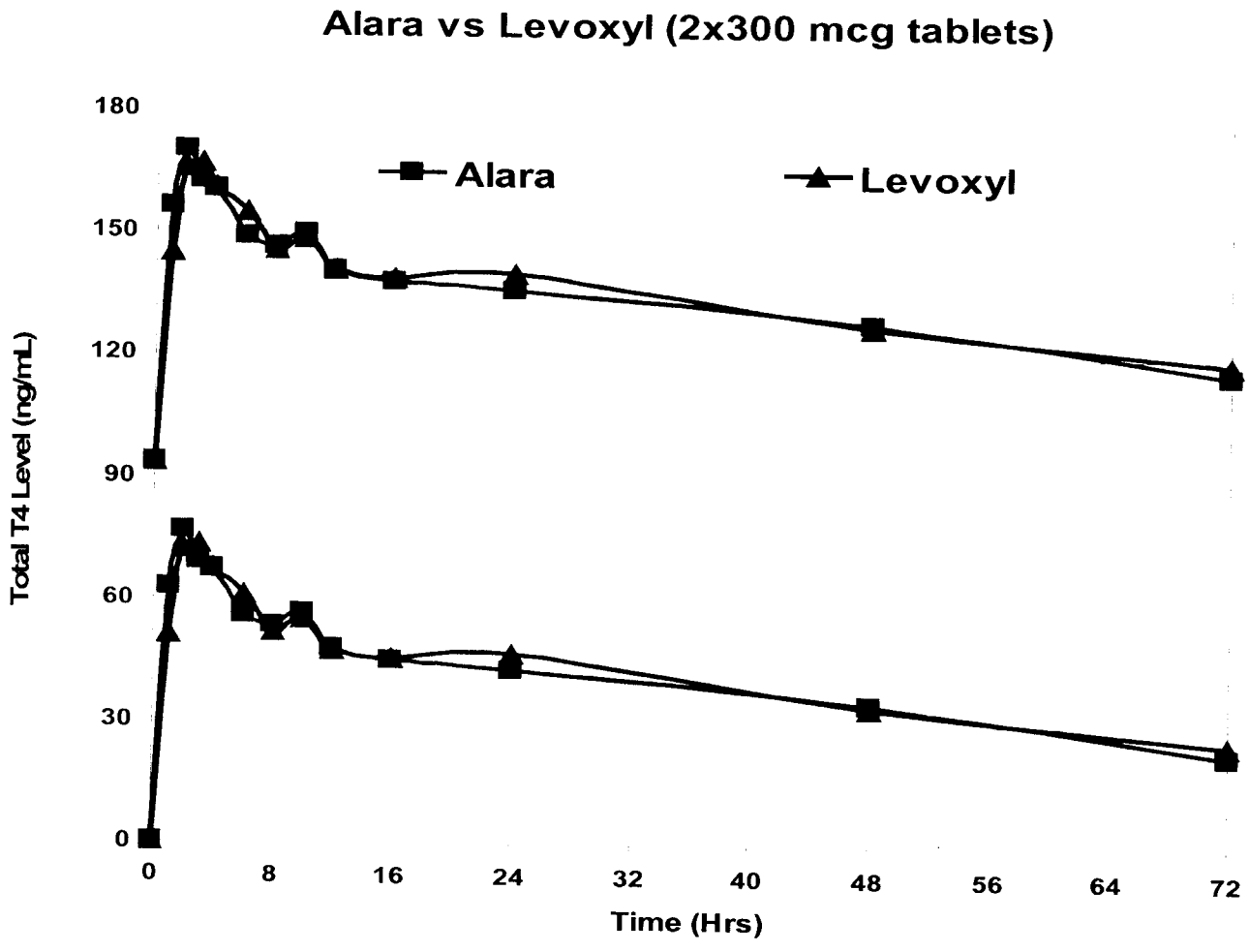

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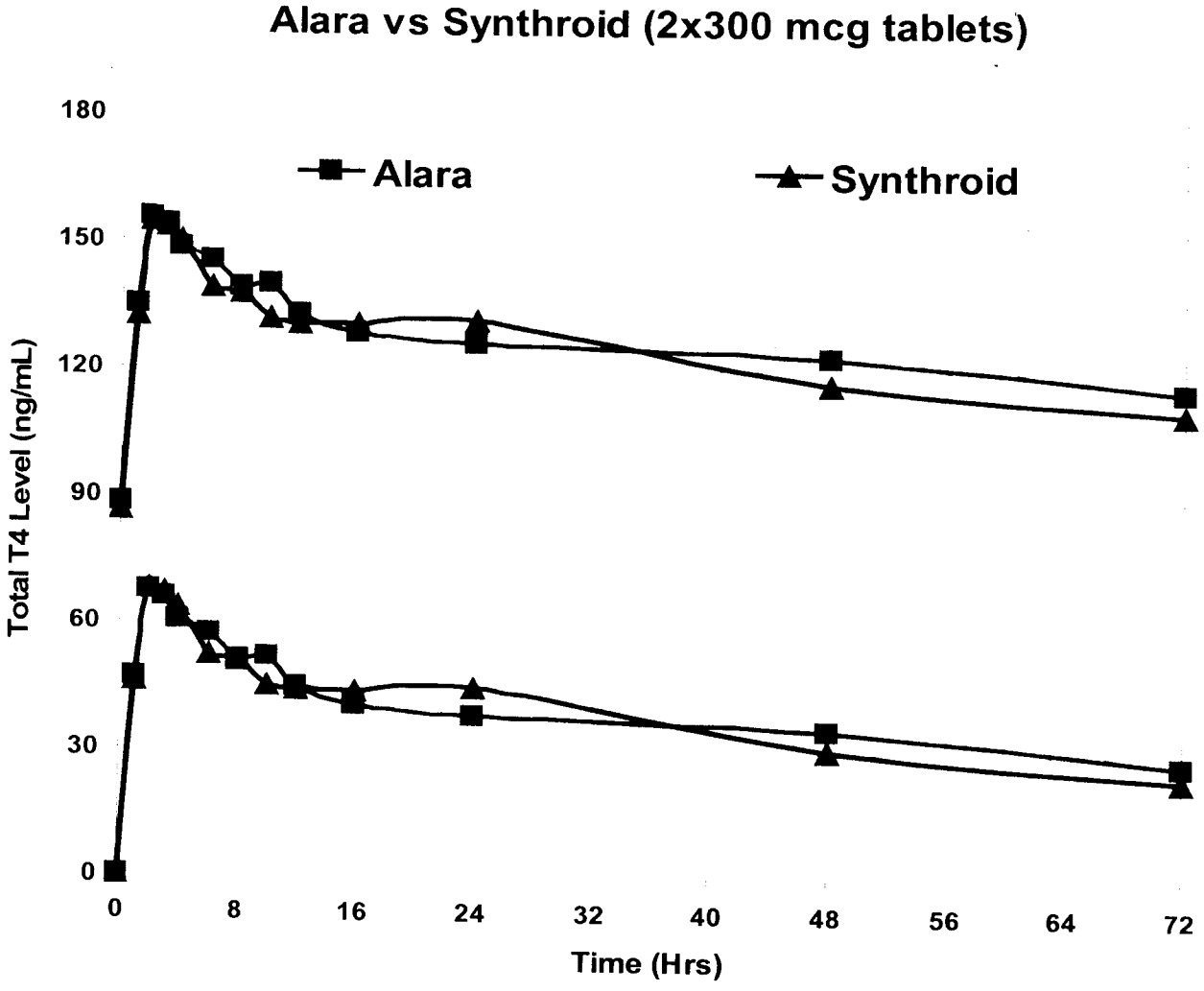

MORE DETAILED RESULTS OF BIOEQUIVALENCE STUDIES:

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ALARA vs SYNTHROID N = 24

	TOTAL CONCENTRATION		ADJUSTED	
AUC	101.3	(99-104)	105.5	(91-122)
C_{max}	101.0	(98-104)	100.4	(93-106)

Dissolution (30 MINUTES)

ALARA	SYNTHROID
97%	93%

ANALYTICAL VARIATION IS APPROXIMATELY 10% (CV):

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EXPECTED CV (ASSUME VARIATION IS ONLY DUE TO ASSAY)

DOSE	**ADJUSTED LEVELS**
600 mcg	20%
300 mcg	38%
150 mcg	44%

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2x300 mcg Tablet Vs. Hypothetical 200 mcg Tablet