STUDY SUMMARY

This randomized, open-label, laboratory-blind, single dose, one-period parallel bioequivalence study was designed to assess bioavailability of BICALUTAMIDE 150 mg Tablets (Synthon Hispania S.L., Spain) versus CASODEX® 150 mg tablets (Astra Zeneca UK Ltd., UK) under fasting conditions. The study consisted of one treatment phase of 648 hours. Parallel design was chosen as R-bicalutamide (the active moiety) is a very long half-live substance.

A total of 72 healthy male subjects were selected for the study according to the inclusion and exclusion criteria and after having given their written informed consent.

In the study group of 72 volunteers there were 72 males between the ages of 18.2 and 50.6 years (median 21.7) and body weights were between 60.4 and 101.9 kg (median 75.9 kg).

The total of 72 subjects received a single oral dose of bicalutamide, all 72 subjects completed the entire study.

According to the study protocol samples of all 72 subjects were analysed and pharmacokinetic parameters were statistically evaluated in balanced design (36 for test product and 36 for reference product).

The study medication, 150 mg bicalutamide in 1 tablet, was administered on June 30, 2004 between 07:00 and 07:34 for Group 1 and on August 02, 2004 between 07:00 and 07:32 for Group 2. Both the test and reference tablets were administered with 240 mL of water under fasting conditions. Blood samples (10 mL) were collected before dosing and at 1.5, 3.0, 4.5, 6, 9, 12, 16, 24, 32, 40, 48, 72, 96, 120, 168, 240, 312, 384, 480 and 648 hours after dosing. After centrifugation the obtained plasma was stored frozen at ≤ -70°C until analysis.

Study medication was well tolerated by all subjects following single oral doses of 150 mg bicalutamide. No serious adverse events were reported during this study; none of subjects withdrew or was withdrawn from the study due to adverse event.

The plasma samples were assayed for bicalutamide (separately for S- and R- enantiomers) using a HPLC-tandem mass spectrometry method developed and validated in laboratories of Quinta-Analytica s.r.o. (Czech Republic). Deuterated bicalutamide was used as an internal standard. The lower limit of quantitation (LLOQ) was 10.0 ng/mL for R-bicalutamide and 1.00 ng/mL for S-bicalutamide.

Samples from all 72 subjects were assayed and the results were subjected to pharmacokinetic evaluation and statistical analysis. The pharmacokinetic parameters derived from the plasma concentrations versus time profiles and the bioequivalence data are presented in the following summary tables.

R-BICALUTAMIDE – SUMMARY OF MEANS

Parameter	TEST		REFERENCE		F	Pr > F
	MEAN	CV (%)	MEAN	CV (%)	(Treatment)	
$AUC_{(0-t)}$ (ng h/mL)	350539.7	17.26	339840.5	27.86	0.33	N.S.
$ln(AUC_{(0-t)})$ (ng h/mL)	12.7526	1.37	12.7003	2.14	0.94	N.S.
$AUC_{(0-inf)}$ (ng h/mL)	361645.7	19.13	353277.4	29.92	0.16	N.S.
$ln(AUC_{(0-inf)})$ (ng h/mL)	12.7809	1.49	12.7344	2.26	0.65	N.S.
C_{max} (ng/mL)	1766.0	14.70	1650.7	17.55	3.17	N.S.
$ln(C_{max})$ (ng/mL)	7.4662	1.94	7.3937	2.42	3.58	N.S.
$ln(C_{max}/AUC_{(0-inf)})$ (h^{-1})	-5.3146	3.53	-5.3407	4.18	0.29	N.S.
t_{max} (h)	37.33	11.46	40.00	39.13	0.97	N.S.
k_{el} (h^{-1})	0.00630	23.14	0.00612	30.64	0.21	N.S.
$t_{1/2e}$ (h)	116.88	27.48	123.12	28.47	0.62	N.S.

Note: S. = significant, N.S. = non-significant at 5% probability level

R-BICALUTAMIDE
SUMMARY TABLE OF THE COMPARATIVE BIOEQUIVALENCE DATA

A single oral administration of one 150 mg tablet of bicalutamide
under fasting conditions (72 subjects)

Pharmacokinetic Parameters TEST versus REFERENCE

Parameter	GEOMETRIC MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
	T	R		Lower	Upper
$AUC_{(0-t)}$ (ng h/mL)	345455.3	327844.9	105.37	96.08	115.56
$AUC_{(0-inf)}$ (ng h/mL)	355347.8	339225.6	104.75	94.92	115.61
C_{max} (ng/mL)	1748.0	1625.7	107.52	100.69	114.82
$C_{max}/AUC_{(0-inf)}$ (h^{-1})	0.0049	0.0048	102.64	94.45	111.56

S-BICALUTAMIDE – SUMMARY OF MEANS

Parameter	TEST		REFERENCE		F	Pr > F
	MEAN	CV (%)	MEAN	CV (%)	(Treatment)	
$AUC_{(0-t)}$ (ng h/mL)	3717.83	20.07	3500.23	34.17	0.86	N.S.
$\ln(AUC_{(0-t)})$ (ng h/mL)	8.2012	2.47	8.1118	3.84	2.08	N.S.
$AUC_{(0-inf)}$ (ng h/mL)	3787.84	19.63	3590.18	33.39	0.71	N.S.
$\ln(AUC_{(0-inf)})$ (ng h/mL)	8.2205	2.43	8.1395	3.73	1.79	N.S.
C_{max} (ng/mL)	110.43	26.47	96.54	26.47	4.61	S.
$\ln(C_{max})$ (ng/mL)	4.6723	5.46	4.5371	5.73	4.96	S.
$\ln(C_{max}/AUC_{(0-inf)})$ (h^{-1})	-3.5482	7.98	-3.6024	9.92	0.51	N.S.
t_{max} (h)	3.67	28.42	4.94	122.85	1.55	N.S.
k_{el} (h^{-1})	0.03346	20.64	0.03344	27.72	0.00	N.S.
$t_{1/2e}$ (h)	21.60	20.98	23.51	53.65	0.73	N.S.

Note: S. = significant, N.S. = non-significant at 5% probability level

S-BICALUTAMIDE
SUMMARY TABLE OF THE COMPARATIVE BIOEQUIVALENCE DATA

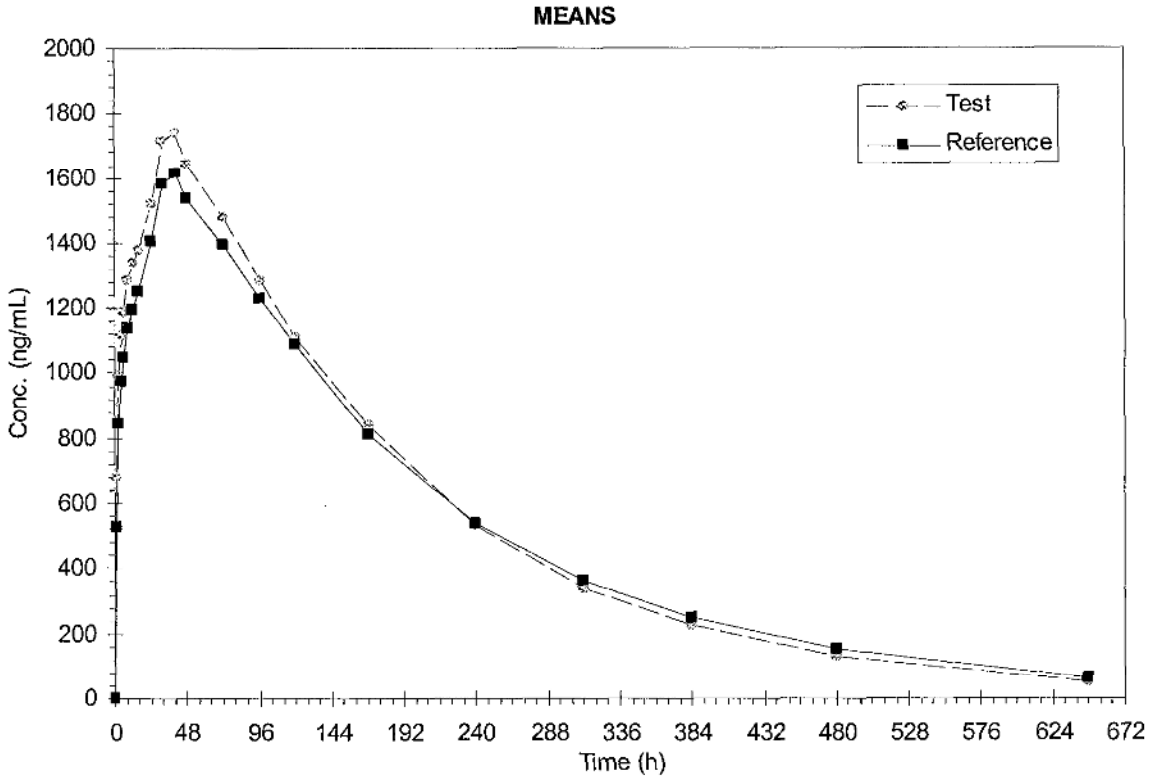
A single oral administration of one 150 mg tablet of bicalutamide
under fasting conditions (72 subjects)

Pharmacokinetic Parameters TEST versus REFERENCE

Parameter	GEOMETRIC MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
	T	R		Lower	Upper
$AUC_{(0-t)}$ (ng h/mL)	3645.22	3333.52	109.35	98.74	121.10
$AUC_{(0-inf)}$ (ng h/mL)	3716.36	3427.30	108.43	97.75	120.28
C_{max} (ng/mL)	106.94	93.42	114.47	103.17	127.01
$C_{max}/AUC_{(0-inf)}$ (h^{-1})	0.029	0.027	105.57	92.68	120.25

Fig.1-2:

R-BICALUTAMIDE CONCENTRATION VERSUS TIME PROFILE OF MEANS (72 subjects)



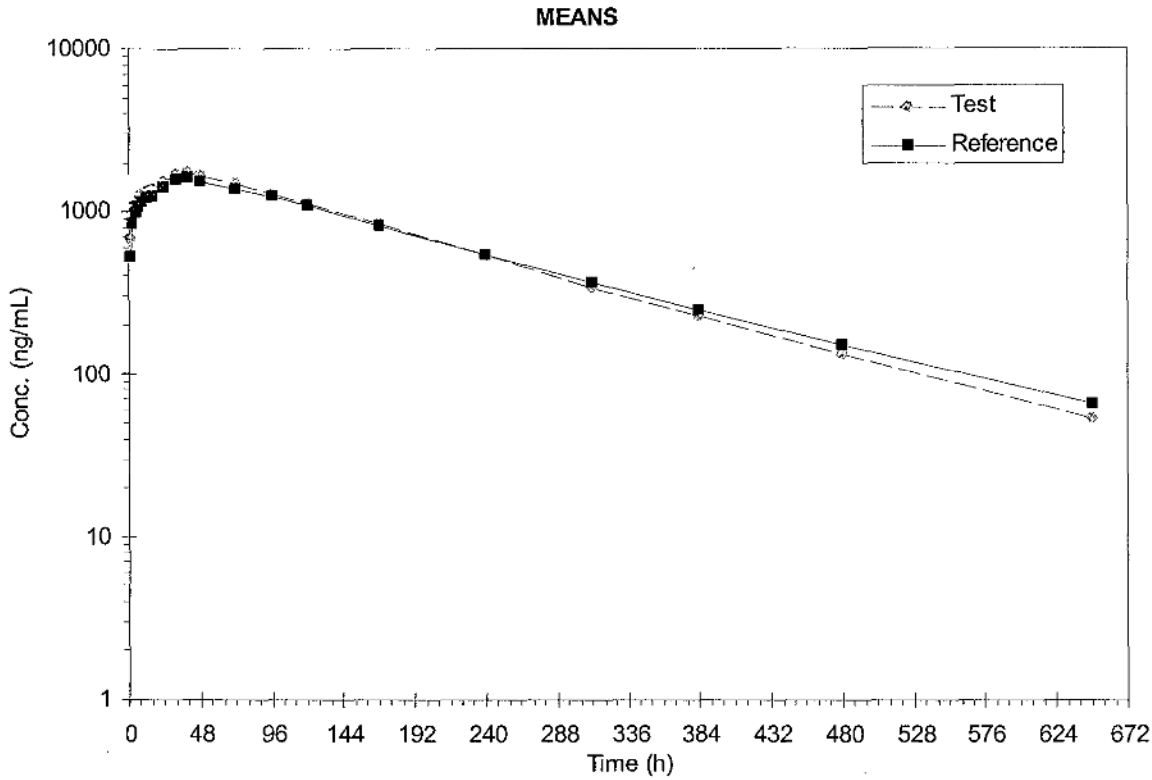
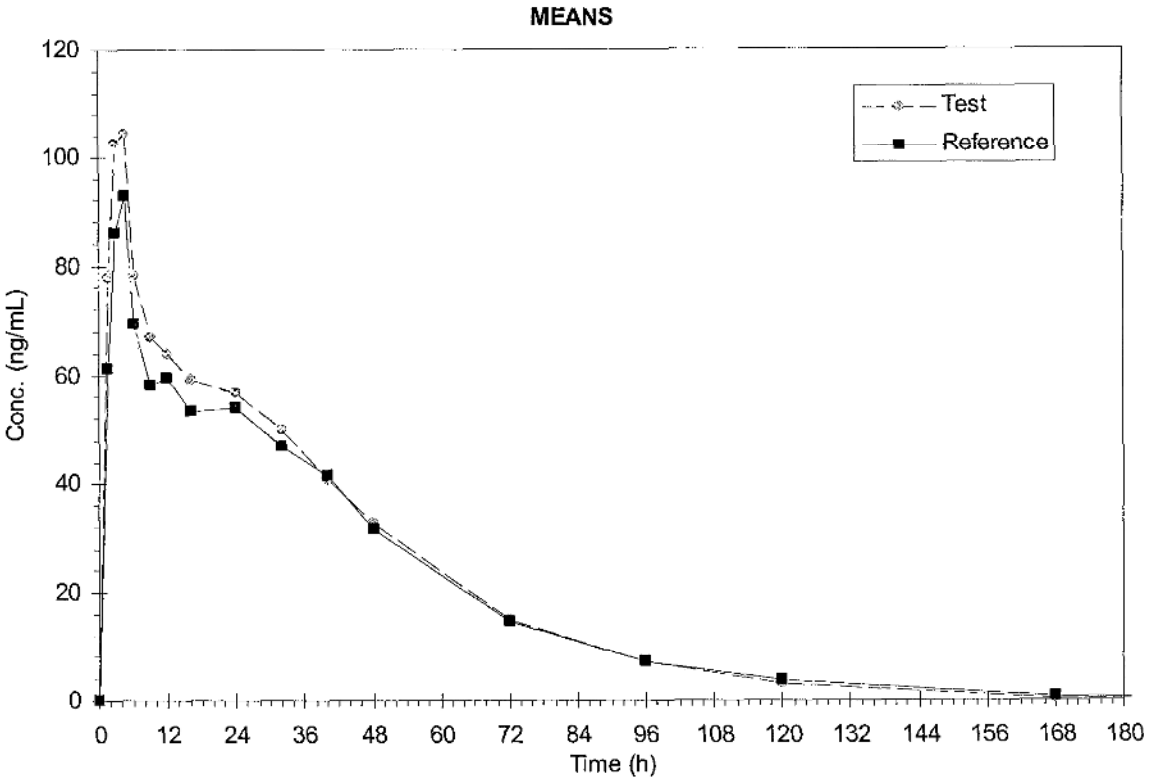
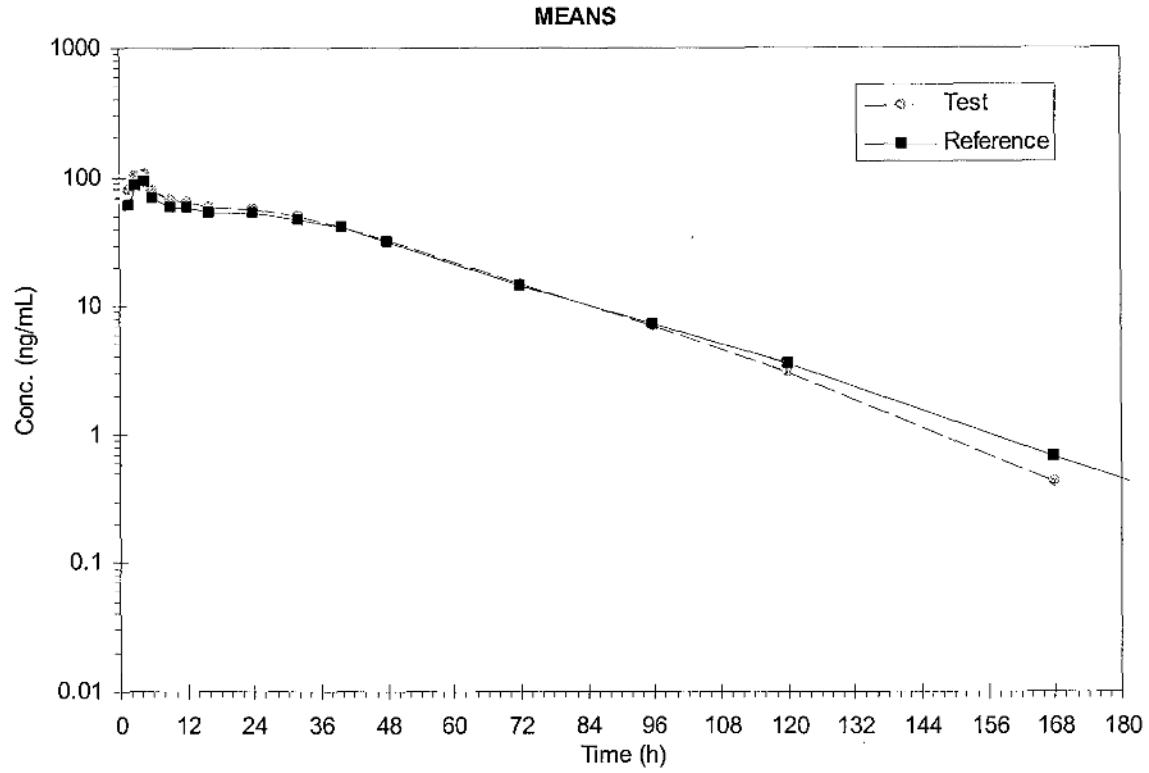


Fig.3-4:

S-BICALUTAMIDE CONCENTRATION VERSUS TIME PROFILE OF MEANS (72 subjects)





CONCLUSION

The objective of the present study was to assess the bioequivalence between BICALUTAMIDE 150 mg tablets (Synthon Hispania S.L., Spain) and CASODEX® 150 mg tablets (Astra Zeneca UK Ltd., UK) under fasting conditions.

According to the protocol, the $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} pharmacokinetic parameters for bicalutamide were used to assess bioequivalence of test and reference products. The results show that the 90% confidence intervals for the geometric mean ratios of Test to Reference formulations for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} were within the acceptance range of 80 to 125%.

Influence of treatment was found non-significant at a 5% significance level for all parameters of R-bicalutamide.

The $AUC_{(0-inf)}$, $AUC_{(0-t)}$ pharmacokinetic parameters for S-bicalutamide as a secondary parameters were also found in bioequivalence acceptance range of 80 to 125%. The C_{max} results for S-bicalutamide exceed the upper limit slightly.

The Test formulation BICALUTAMIDE 150 mg tablets was found to be bioequivalent to the Reference formulation CASODEX® 150 mg tablets.

Study medication was well tolerated by all subjects following single oral doses of 150 mg bicalutamide.