Appendix II: Name and Address of Study Director

[redacted]
Institut für Humanpharmakologie, Schering AG
[redacted]

Appendix III: Trial Protocol and Amendments

Total no. of pages: 25
Date: 03.09.92

Bioequivalence Trial of Oral Application of ANDROCUR 100 mg Tablets as Compared to Two ANDROCUR 50 mg Tablets in 36 Young Men

Confidential

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Date: 8 Oct 1992

Overview

Trial title:	Bioequivalence Trial of Oral Application of ANDROCUR 100 mg Tablets as Compared to Two ANDROCUR 50 mg Tablets in 36 Young Men
Trial aims and parameters:	Bioequivalence of cyproterone acetate in one tablet ANDROCUR 100 mg and two tablets ANDROCUR 50 mg AUC $_{0\text{-}24h}$, C_{max}, t_{max} of cyproterone acetate
Trial design:	open, intra-individual, crossover, random
Trial substance, Dosage, Application:	ANDROCUR 100 mg, 1 tablet, oral ANDROCUR 50 mg, 2 tablets, oral
Number of trial groups:	1
Number of volunteers:	36 young men
Project number:	
SH - No:	
ZK - No:	
Generic name:	Cyproterone acetate

Trial preparation data

Manufacturer	Schering AG
Trade name	not applicable
ZK-No.	9471
SH-No.	T 548 A
Generic name	Cyproterone acetate
Chemical name	17-Acetoxy-6-chloro-1a,2a-methylene-4,6-pregnadiene-3,20-dione
Drug form	tablet
Concentration	100 mg
Unit dose	100 mg
Radioactive unit dose	not applicable
Packaging	glass jar
Specific Galenic data	none
Labelling	Trial directol 1 tablet for internal use Schering AG, Berlin/Bergkamen For clinical trials only
Storage	Trial preparations will be stored in a safe place at room temperature.
Return	The use and location of test preparations is to be documented. All containers, including left-over test preparations\containers, are to be turned over to ZV-Lagerverwaltung for disposal at the end of the trial. The whereabouts of missing containers/test preparations are to be explained in writing.

Control preparation data

Manufacturer	Schering AG
Trade name	ANDROCUR®
ZK-No.	9471
SH-No.	
Generic name	Cyproterone acetate
Chemical name	17-Acetoxy-6-chloro-1a,2a-methylene-4,6-pregnandiene-3,20-dione
Drug form	tablet
Concentration	50 mg
Unit dose	50 mg
Radioactive unit dose	not applicable
Packaging	glass jar
Specific Galenic data	none
Labelling	Ex Trial directc 2 tablets for internal use Schering AG, Berlin/Bergkamen For clinical trials only
Storage	Control preparations will be stored in a safe place at room temperature.
Return	The use and location of control preparations is to be documented. All containers, including left-over control preparations/containers, are to be turned over to ZV-Lagerverwaltung for disposal at the end of the trial. The whereabouts of missing containers/control preparations are to be explained in writing.

Formalities

Are resolutions 3,4,5, or 6 on hand?	Resolution: 5	dated: 04.04.90
Is internal Schering authorization required (by filing an application)?	yes	
Are the documents on file at the Ministry of Health?	yes	Nr. 142/40 BGA dated: 01.10.91
To be filed at a future date?	no	
Is notification of the Senator for Health and Human Services obligatory?	yes	
Is volunteer insurance obligatory?	yes	
Inspection by the IRB/Medical Council Ethics Committee?	yes	
The trial takes place under QAU supervision.	yes	

Responsibilities

Task/Function	Name	Name	Signature/Date
Trial planning:	(physician)	(chemist/ biometrician)	
Specific volunteer information:	(physician)		
Initial and final volunteer examinations:	(attending physician)	(physicians)	
Experimental duties:	(attending physician)	(tech. staff)	
Laboratory analyses:			
Main laboratory:	(med. director)		
Spermiogram	(tech. staff)		
Cyproterone acetate	(to be entered)		
Pharmacokinetics:	(chemist)		
Administrat./Documentation:	(tech. staff)		
Quality control:	(tech. staff)		
Data evaluation:	(tech. staff)	(biometrician)	
Report:	(physician)		
Contractor: SCHERING represented by	Head of Human Pharmacology		
Clinical Trial Director:	(physician)		

Trial site

Schering AG, Humanpharmakologie [illegible] Dept. Herz-Kreislauf, Diagnostik, Zentrallabor Humanpharmakologie.

Time frame

Those appointments that are indefinite or can not be planned before the time frame is created must be declared in the form "Trial protocol change/amendment No.:" at the latest shortly before the beginning of the trial phase as listed below:

	Date
Berlin Medical Council Ethics Commission:	24. 09. 1991
Trial begins:	14. 10. 1991
Trial ends:	12. 11. 1991
Number of treatment days:	2
Evaluation by:	I/1992
Biometric evaluation by:	I/1992
PHRR draft turned in to QAU:	II/1992
Completion of PHRR:	II/1992

Table of Contents

1. Introduction

Cyproterone acetate (CPA) is a steroid hormone with anti-androgenic properties, which is used in the treatment of prostate carcinoma. The commercial preparation ANDROCUR® contains 50 mg CPA. Daily dosages lie between 100 and 200 mg for castrated patients, and between 200 and 300 mg for patients who are not castrated.

To ease intake of the substance and to improve patient "compliance", a new ANDROCUR tablet has been developed, which contains 100 mg CPA.

In earlier pharmacokinetic studies, a radio-immuno-assay was used to determine the plasma level of CPA. Although this method is very sensitive, the detection limit is approx. 50 pg/ml, it is not entirely specific, the RIA shows cross-reactions (approx. 20%) with the main metabolite CPA 15ß-hydroxy cyproterone acetate.

Because of this, the HPLC method was used in later trials as a new analytical technique which allows for the simultaneous measuring of CPA and 15ß-hydroxy cyproterone acetate levels. The AUC values which were compiled using the HPLC method were approx. 50% lower than those statistics obtained using the RIA method. Because the HPLC method has a comparatively higher detection limit of 50 ng/ml, it is only used with high dosages of CPA.

A trial examining the bioequivalence of 100 mg tablets of ANDROCUR as opposed to two 50 mg tablets of ANDROCUR® has already been conducted with 17 men. The HPLC method was used for determination of CPA levels.

The main criterion for bioequivalence is the surface under the curve (AUC) and the time (t_{max}) and the height (C_{max}) of the maximum serum level. The trial results showed that the two formulations were not bioequivalent according to the definition of the registration authorities (German Federal Health Office) The cause was the unexpectedly large degree of intra-individual variance in the AUC values of CPA, which possibly has methodological reasons.

The aim of the planned trial is to reexamine the bioequivalence of the new ANDROCUR 100 preparation compared to the commercially available preparation ANDROCUR® 50 with a higher number of cases and using a more sensitive detection method to test for CPA. The required group size (n= 36 men) was statistically calculated. The specific and sensitive GC/MS method for detection of CPA levels was chosen.

A list of trial-relevant data used, e.g. PH Research Reports, historic and bibliographic data, can be found in the trial documentation.

1.1 Trial aim and hypotheses

Trial aim:

Trial of the bioequivalence of ANDROCUR 100 mg and ANDROCUR® 50 mg formulation by determination of the pharmacokinetic parameters ($AUC_{0 - 24\ h}$, C_{max}, t_{max}) of the active ingredient cyproterone acetate.

Trial hypothesis:

One tablet of ANDROCUR 100 mg and two tablets of ANDROCUR® 50 mg are bioequivalent.

The main and accompanying parameters are detailed in section 2.5 (Biometric Planning and Evaluation.)

1.2 Design

The trial will be conducted as an open randomized, intra-individual comparison with two treatments.

The two treatments are 1 x 1 tablet ANDROCUR 100 mg and 1 x 2 tablets ANDROCUR® 50 mg. Every volunteer will be given both treatments (n = 36, 4 blocks of 9 volunteers).

The treatments will be given at 21 day intervals.

The duration of the trial after each treatment will be 5 days.

2. Methods

2.1 Volunteers

2.1.1 Inclusion criteria

Volunteers who take part in the trial must meet the following criteria:

- Age: 20-45 years
- Sex: male
- Body weight should not exceed or fall below the following value:

  Height in cm minus 100= weight in km +/- 20%
- Physical condition: The volunteers must be in good physical condition. This will be determined through the physical and laboratory examinations and the anamnesis.
- belonging to a specific ethnic group is unimportant

2.1.2 Restrictions During The Trial

- Smoking — not permitted
- Alcohol consumption — not permitted
- Physical activity — strenuous physical activity is not permitted during the trial
- Additional therapy — not permitted
- Standardized food and beverages must be consumed on treatment days.

2.1.3 Exclusion criteria

Volunteers will be restricted from the trial according to the following criteria:

- Volunteers with azoospermia (with the exception of those who are sterilized)
- Volunteers who are Hepatitis antigen carriers (HBsAG or Hepatitis B test), or HIV positive
- Volunteers who, within one week before the beginning of the trial, have used systemic or local medication, which could interfere with or influence the trial aim
- Volunteers whose anamnesis suggests drug or alcohol abuse
- Volunteers on special or exclusive diets, e.g. strict vegetarian, low calorie diet
- Volunteers with known allergic reactions to cyproterone acetate or to components of the galenic preparation
- Volunteers with an anamnesis of severe, acute gastrointestinal illness within the past 30 days.
- Volunteers with previous or current thrombembolic processes
- Volunteers whose absorption, distribution and excretion of medication can be assumed to be abnormal, due to a history of or current symptoms in the gastrointestinal tract, liver, kidneys, or endocrinic, respiratory or circulatory systems
- Volunteers whose absorption, distribution and excretion of medication can be assumed to be abnormal, due to the presence of glaucoma, of changes in the blood, or changes in the peripheral or central nerves.
- Volunteers who have been severely ill within the four weeks preceding the beginning of the trial
- Volunteers who have undergone severe physical duress within 14 days before the beginning of the trial
- Volunteers who, in the opinion of the clinical trial director or the initial examination physician, should not participate in the trial

2.1.4 Pre-trial examinations[1]

Before the beginning of the trial, an HIV- and HBsAG-test (the HIV- and HBsAG-test may not be older than 3 months) and a drug screening[2] test will be performed if necessary.

Within 3 weeks before the beginning of the trial, every volunteer will undergo an internal and laboratory examination. A spermiogram will also be performed on each volunteer.[3]

2.1.5 Post-Trial Examinations

The chemical analyses will be repeated at the latest one week following the end of the trial and a spermiogram will be performed within two weeks of the trial end. A final internal examination is **not** necessary.

2.1.6 Blood sampling, blood loss

The total amount of blood to be drawn during the 27 day trial is 192 ml, as well as 40 ml for the pre-trial and post-trial examinations.

2.1.7 Probation

Volunteers are not to participate in further trials within 1 month following individual trial completion.

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[1]The following parameters will be screened as part of the **initial** and **final** volunteer examinations.

Hematology and Clinical chemistry:

alpha-Amylase	Urea	Cholesterol
LDH	Electrophoresis	Triglycerides
Alkaline phosphatase	Total protein	Blood sugar
Gamma-GT	Calcium	Urine status:
GOT	Chloride	- Urobilinogen
GPT	Potassium	- Erythrocytes
Cholinesterase	Sodium	- Hemoglobin
LAP	Quick	- Protein
Total bilirubin	Fibrinogen	- Ketones
Creatinine	PTT	- Bilirubin
Anorganic phosphate	Total blood count	- Nitrate
Uric acid	Total iron	- Glucose

Volunteers will be informed of any and all deviations of a pathological nature, and instructed to contact their personal physician. Volunteers are excluded from participation whenever lab findings, in medical opinion, suggest disease

All necessary examinations will be performed b[illegible]
and Hämatologie will be [illegible]

[2]The ***drug screening*** will include **cannabinoids, opiates, amphetamines, barbiturates, cocaine, benzodiazepine** und **methadone.**

The evaluations will be performed by th[illegible]

*The MDL as well as t[illegible]

[3]The spermiogram will be conducted in [illegible]

2.1.8 Standard volunteer stipulations

2.1.8.1 Volunteer information

Each volunteer will receive oral and written information (General Volunteer Information). Each volunteer who participates in the trial will receive oral clarification of the trial; he will also receive a printed copy of Specific Volunteer Information as well as a copy of his signed consent form. Volunteers will be given an updated copy of General Volunteer Information upon request.

Volunteer selection will take place in accordance with the revised Helsinki Declaration, 1989 Hong Kong amendment and §§40/41 of the German Drug Law.

Volunteers will be randomly selected from the Central Volunteer File according to established inclusion and exclusion criteria, then called or written to.

2.1.8.2 Volunteer insurance

Volunteers are insured in accordance with German Drug Law. Volunteer insurance will be arranged by

ıe basis of an "Application for the Execution of a Clinical Trial" (number of volunteers).

2.2 Treatment and randomization

Application/treatment will be performed under the supervision of a member of the trial staff. This staff member will assure and document that the volunteer receives treatment as planned.

2.2.1 Explication of the treatment schedule

The trial will consist of a treatment group with 36 participants (4 blocks of 9 volunteers.)

The trial substances will be cyproterone acetate in the form of ANDROCUR® 50 and ANDROCUR 100 mg tablets.

The trial substances will be applied in 21 day intervals.

2.2.2 Treatment schedule

Treatments:

Treatment A: one tablet SH T 548 A at 100 mg

Treatment B: two tablets SH 8.0714-50 MG at 50 mg each

The two treatments will be given to the volunteers in the morning as of 8:00. They will be taken on an empty stomach with 100 ml of non-carbonated mineral water.

2.2.3 Randomization and decoding

The randomizations list was prepared by the Institut für Biometrie (D

Explanation:

Block:

1 = Block 1

2 = Block 2

Treatment:

1 = 1x100 mg

2 = 2 x 50 mg

Order:

1 = 1 x 100 mg / 2 x 50 mg

2 = 2 x 50 mg / 1 x 100 mg

Volunteers 1 - 9 will be treated on the first trial day (block 1), volunteers 10 - 18 on the second trial day (block 1), volunteers 19 - 27 on the third trial day (block 2) and volunteers 28 - 36 on the fourth trial day (block 2) of each treatment.

Randomization list:

Volunteer	Order of Treatments		Block
1	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
2	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
3	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
4	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
5	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
6	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
7	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
8	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
9	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
10	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
11	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
12	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
13	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
14	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
15	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
16	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 1
17	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
18	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 1
19	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
20	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
21	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
22	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
23	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
24	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
25	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
26	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
27	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
28	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
29	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
30	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
31	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
32	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
33	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
34	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2
35	1 x 100MG ANDROCUR	2 x 50MG ANDROCUR	Block 2
36	2 x 50MG ANDROCUR	1 x 100MG ANDROCUR	Block 2

2.3 Research methods

2.3.1 Methods to insure volunteer safety

Laboratory-chemical "safety" parameters will not be determined because there is ample data available as to the safety and tolerance of the active ingredient cyproterone acetate since it was introduced in 1973 and has been used since as an antiandrogen.

The volunteers will be asked how they are feeling before each of the two treatments.

They will be asked to immediately inform the trial personnel of any concomitant events ("adverse events") during the entire trial. Every event reported by a volunteer who is undergoing treatment will be entered on data record forms:

volunteer

treatment

reported event

beginning (day/hour/minute after application of the trial substance)

duration (day/hour/minute after application of trial substance)

intensity[4]

correlation to trial substance[5]

2.3.1.1 Drug screening during treatment

Drug screening will be performed before every treatment (test point 1). The same drugs will be screened for as those during the pre-trial examination.

2.3.2 Methods to achieve the trial aims

At specific times 6 ml of blood (2.5-3 ml serum)[6] will be drawn and centrifuged after one-half hour to determine the agent level of cyproterone acetate. The collected serum will be frozen until it is analyzed. The serum samples will be analyzed at [redacted] e agent will be determined with the CG/MS method. The results will be [redacted] by [redacted]

[4] 1 = mild; 2 = moderate; 3 = severe

[5] 1 = none; 2 = possible; 3 = definite

[6] only at test point 1 will 12 ml of blood (at least 5 ml of serum) be drawn

2.3.3 Methods and scheduling

SYMBIOS - STUDY OUTLINE OF TARGETS AND TESTPOINTS; STATUS: MATRIX DEFINITION

SYMBIOS CATALOG-VERSION 910910.S31

STN: 91089

(c)SYMBIOS 1986-1990; printed: 10-SEP-91

TESTTIME--->

TG	ITEMNAME	ITEM															
		DAY------>	0	0	0	0	0	0	0	0	0	0	1	2	3	4	5
		HOUR----->	0	0	1	1	2	3	4	6	8	12	0	0	0	0	0
		MINUTE--->	0	30	0	30	0	0	0	0	0	0	0	0	0	0	0
		SECOND--->	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		TESTPOINTS:															
A	CYPROTERON-ACETATE;SERUM	C309	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A	BLOOD SAMPLING	H011	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A	DRUG ADMINISTRATION P.O.	H001	1														
A	AMPHETAMINE; URINE	A401	1														
A	BARBITURATE; URINE	A402	1														
A	BENZODIAZEPINES; URINE	A403	1														
A	CANNABINOIDS; URINE	A404	1														
A	COCAINE; URIN	A405	1														
A	OPIATES; URINE	A406	1														
A	METHADONE; URINE	A407	1														

END OF SYMBIOS - STUDY OUTLINE OF TARGETS AND TESTPOINTS; OUTLINE PRINTED 10-Sep-91 12:6

2.4 Daily schedule

2.4.1 Volunteer accommodations (see also daily schedule chart)

Overnight stay:	before treatment days (day -1)
Daytime accommodations:	a maximum of 13 hours on treatment days (day 0)
	a maximum of 1 hour on examination days (days 1-5)

2.4.2 Volunteer care

On the treatment days (day 0), the volunteers will receive a light breakfast as of 10:00: 2 rolls, 40 g butter, 25 g sausage, 25 g jelly, 250 ml coffee substitute

As of 12:00 a standard lunch (frozen food: beef roll-up, red cabbage, potatoes), as well as 200 ml fruit yogurt and 250 ml non-carbonated water will be served.

At 16:00 the volunteers will receive "afternoon coffee": 1 piece of fruit cake, 250 ml coffee substitute.

As of 19:00 dinner will be offered: 3 slices of bread, 40 g butter, 75 g cold cuts, tomatoes/cucumbers/green pepper slices, 250 ml non-carbonated water).

2.4.3 Additional information

The 36 volunteers in a treatment group will be treated in four blocks of nine participants on four consecutive days.

The nine volunteers in one block will arrive around 21:00 on the evening prior to the treatment days (day -1) at Humanpharmakologie and spend the night there (no food or drink after 22:00 p.m.).

On the following morning (7:00) they will go to the trial unit. The volunteers will be asked how they are feeling. They will empty their bladders. A drug test will be carried out on the urine sample. An indwelling cannula will be placed in a forearm vein and a blood sample will be drawn for the determination of pre-treatment values.

The trial substance will be applied to the volunteers between 8:00 and 8:30. The nine volunteers will be treated at two minute intervals.

After this, blood samples will be drawn for a period of 12 hours. After the final sample the volunteers will be dismissed.

The volunteers will appear in the trial unit as of 7:30 on the five following examination days. They will be asked how they are feeling. As of 8:00 a blood sample will be drawn.

2.4.4 Daily schedule chart

Day	Test point	Time after application	Real time	Measure
-1			21:00	volunteer arrival overnight stay
0	1		as of 7:00	urine (drug test), indwelling cannula, blood sample, questioning
			8:00	begin application of trial substance to first volunteer
	2	30 minutes	8:30	blood sample[7]
	3	60 minutes	9:00	blood sample
	4	90 minutes	9:30	blood sample
	5	2 hours	10:00	blood sample, followed by standard breakfast
	6	3 hours	11:00	blood sample
	7	4 hours	12:00	blood sample, followed by standard lunch
	8	6 hours	14:00	blood sample
	9	8 hours	16:00	blood sample, followed by "afternoon coffee"
			19:00	standard dinner
	10	12 hours	20:00	blood sample, followed by dismissal of volunteers
1			as of 7:30	volunteer arrival, questioning
	11	24 hours	8:00	blood sample
2			as of 7:30	volunteer arrival, questioning
	12	48 hours	8:00	blood sample
3			as of 7:30	volunteer arrival, questioning
	13	72 hours	8:00	blood sample
4			as of 7:30	volunteer arrival, questioning
	14	96 hours	8:00	blood sample
5			as of 7:30	volunteer arrival, questioning
	15	120 hours	8:00	blood sample

[7] from first volunteer

2.5 Biometric planning and evaluation

2.5.1 Target parameters

The main target criterion for bioequivalence is the area under the concentration time curve AUC_{0-24h} of cyproterone acetate. Additional target criteria are the maximal achieved serum level (C_{max}) and the time of the highest serum level (t_{max}).

2.5.2 Hypotheses

Within the framework of this bioequivalence study, the null-hypothesis

H_0: The area under the concentration curves AUC_{0-24h} of cyproterone acetate after oral administration of 100 mg tablets or correspondingly two 50 mg tablets are not equal, i.e.

$$\mu_{100} - \mu_{50} \leq -\theta_1 \text{ or}$$

H_0:

$$\mu_{100} - \mu_{50} \geq \theta_2$$

will be compared to the alternative hypothesis

H_1: the AUC_{0-24h} of cyproterone acetate after oral administration are equivalent, i.e.

H_1: $\theta_1 \leq \mu_{100} - \mu_{50} \leq \theta_2$

2.5.3 Statistical evaluation

The characteristic AUC_{0-24h} will be transformed for the calculation of the bioequivalence ln, the equivalence interval fixed at (θ_1 = ln 0.8, θ_2 = ln 1.25). The hypotheses 2.5.2 will be compared to the interval method, i.e. the position of the usual confidence interval regarding the confidence niveau (1 - 2 α,α = 0.05) for (μ_{100} - μ_{50}) will be related to the equivalence interval (Schuirmann 1987).

Under the assumption that the new determination method for CPA (GCMS method) produces smaller residual variance, 36 men in the changeover trial design are sufficient to make possible the proof of bioequivalence of a 100 mg tablet compared to 2 x 50 mg tablets.

Additional target criteria will be analyzed accordingly.

2.5.4 Dropouts

If a volunteer drops out for reasons unrelated to the trial, he will be replaced if possible.

The replacement volunteer will receive all treatments.

The medication as well as the samples collected from the replacement volunteer will receive a number that has been increased by 40 (for example, 42 if volunteer number 2 drops out, 57 for volunteer number 17).

The data for discontinued volunteers will be documented in the trial records.

2.6 Storage, labelling, etc. of biological material

Collected samples will be labelled with trial number, volunteer number, treatment and test point.

Samples that are not immediately analyzed will be stored at -18°C until processing.

2.7 Strains and risks

2.7.1 Strain/Risks due to the trial structure

Vein puncture during blood sampling may be accompanied by slight bleeding and in rare cases by a temporary inflammation of the wall of the vein. After initial irritation, the presence of the plastic cannula is generally painless and practically unnoticed.

2.7.2 Strain/Risks due to the trial preparation

The bioequivalence trial of two ANDROCUR formulations presented here is necessary for the following reasons: the daily dose in the treatment of prostate carcinoma can be as high as 300 mg, i.e. 6 tablets of ANDROCUR. Because this illness usually effects older patients, who often must take several medications, a reduction in the number of tablets which must be taken each day can be a relief to the patients. In addition, experience has shown that the reliability of taking medications drops with the number of tablets. Success in the treatment of prostate carcinoma can therefore be jeopardized by missed or irregular drug taking.

In this trial, the volunteers receive two single doses of ANDROCUR (100 mg each) three weeks apart.

Cyproterone acetate has effects on the regulatory cycle of pituitary glands. As a highly effective progestagen, the substance has an antigonadatropic effect, which is, however, weakened in males. A temporary effect on pituitary gland function, for example a reduction of peripheral sexual steroids - is possible with a single administration, however this is only serologically determinable and without clinical relevance.

Tests show that the concentration of testosterone sinks with ANDROCUR, but that with it rises again with extended continuous administration.

Only after extended use of ANDROCUR can changes in body weight and libido, tension in the chest, tiredness, a reduced ability to concentrate as well as depressive moods temporarily occur. These concomitant events are, however, not to be expected after a single administration of ANDROCUR.

As an antiandrogen, cyproterone acetate inhibits spermatogenesis.

Doses of 50 - 200 (-300) mg ANDROCUR/day as they are used therapeutically, have led over the course of several weeks to a reduction of the male sperm count as well as the percentual share of sperm in normal mobility and character.

Normal spermiogram results were found about 3-6 months after the discontinuation of treatment - partially carried out over a period of years - with these dosages.

Even low dosages down to 5 mg cyproterone acetate/day, which were administered to volunteers for several months, caused biochemical spermiogram changes which are characteristic for sub- and infertility. These, too, were fully reversible after discontinuation.

An effect on spermatogenesis is not to be expected after a single administration of ANDROCUR. A spermiogram will, however, be performed before the beginning and after the end of the trial.

The administration of ANDROCUR does not comprise a specific risk to volunteers, because all findings correlating with cyprotene acetate's temporary pharmacological influence on the androgen regulatory cycle are not demonstrable after a single administration and are always fully reversible after mutiple administrations.

After the evaluation of benefit and risks, trial performance is considered to be ethically sound. The trial protocol will be submitted to the appropriate Ethics Committee for approval.

2.7.2 Evaluating adverse events/effects

Adverse events or effects will either be reported by the volunteer or observed/noted by one of the trial staff. This is to be documented accordingly.

Adverse events or effects are to be evaluated according to **intensity** as indicated below:

1 = "mild"	The event does not interfere with normal volunteer functions, but is perceived by the volunteer as bothersome.
2 = "moderate"	The event impairs volunteer function to some extent (uncomfortable or embarrassing), but does not threaten his health.
3 = "severe"	The event represents a clear danger to the volunteer's health; unmistakable damage to volunteer functions or capabilities.

Evaluating the degree of likelihood of a **correlation** between an adverse event or effect and **the test preparation** is to be graded as follows:

1 = "none"	No causal and/or time correlation time between event and trial preparation.
2 = "possible"	The event correlates temporally with the application of the trial preparation, but other causes for this effect are conceivable.
3 = "definite"	The event correlates temporally with the application of the trial preparation, and there is no other plausible explanation for its occurrence.

2.7.4 Trial discontinuation

2.7.4.1 Criteria for the discontinuation of the entire trial

- Unexpected (according to the present level of knowledge) events, contingent on the trial substance cyproterone acetate, which occur regularly with many participating volunteers. The following evaluation criterion applies:

  Evaluation of unexpected events: "severe"

2.7.4.2 Criteria for the discontinuation of individual volunteers

- Unexpected events which occur repeatedly:

  Evaluation of unexpected events: "severe",
- Circulatory collapse during cannula insertion or blood sampling,
- Proof of drugs or disallowed medications during the trial,
- Failure to uphold trial conditions,
- Withdrawal of informed consent.

2.8 Emergency procedures

- The clinical trial director is to be immediately summoned or informed of all severe adverse events.
- In double-blind trials: The emergency envelope will be made available for immediate inspection by the clinical trial director in case of emergency.
- Attention is to be paid to adverse events for the duration of the trial. Should these occur, volunteer safety takes foremost priority and medical measures are to be taken wherever necessary.
- The immediate treatment of adverse events should take place symptomatically. Emergency medical equipment will be made available as needed.
- Severe adverse events must be reported by the clinical trial director within the specified time to the Head of Humanpharmakologie, the Stufenplanbeauftragten, the responsible

authorities, the responsible Ethics Committee and, if necessary, the FDA. In addition, all severe adverse events are to be clearly documented.

2.9 Documentation and archiving information

- Documentation will be carried out in such a way that future reconstruction of trial events (in accordance with trial protocol specifications) will be clear and easy. The file plan will be used.
- Trial data include all findings, measurements, other individual data, photos, measuring strips, summaries, etc. in paper form. All data stored in electronic data retrieval systems for the trial are to be made available in dated hard copy and initialed by those staff responsible for the trial. Electronic data are not considered originals, but may be archived in addition to the trial documentation.
- Following the completion of Specific Volunteer Information, consent forms will be signed by the volunteer and the clarifying physician, then stored in the trial file. The volunteer will receive a copy.
- The use of test preparations will be carried out and documented by a designated member of the trial staff.
- Electronic data are to be marked clearly with the trial number/data type/date/hard and software information.
- Trial documents produced or available in paper form (e.g. raw data on data forms, trial sheets, informal papers, printouts, etc.) are to be noted with trial number/data/type/date/initials of trial staff involved.
- Trial data will be documented in the SYMBIOS documentation system.
- Following trial completion, trial documents are to be organized according to the Trial Master File and turned over to Ref. Dokumentation.
- The minimum provisional length of time for which trial documents are to be archived is at least 15 years.
- Any deviation from the trial protocol in trial planning or execution is to be documented after presentation of the final version of the trial protocol on a separate form, "Change/amendment of trial protocol", including reason, content, grounds, consequences, date and the clinical trial director's signature. Trial staff will then be informed by distribution of a copy.
- Deviations from the trial protocol during the trial must be documented with reasons and point in time.

2.10 Quality control and assurance

A staff member involved in the trial will check the collected data for the purpose of quality control regarding correctness, completeness and legibility of entries.

An independent quality assurance unit will audit the trial protocol, the conducting of the trial and the PH research report to ensure that the trial was conducted in accordance with GCP standards.

Appendix IV: Case Report Forms

Table of Contents

SYMBIOS DATASHEET (c)1986-1990 SYMBIOS I; CV: 920427.S31 STUDY-NUMBER: 91089;

TREATMENT: A SUBJECT-NUMBER: 1
ITEMNAME: BLOOD SAMPLING
ITEM: H011 INAME : BLOS
NORM RANGE: 0 - 1 SCORE INDEX

METHOD: 0: NOT DONE, 1: DONE

INITIAL EXAMINATION:			FINAL EXAMINATION:		COMMENTS:
DTP: d0 h0 m0 s0	DTA:	RESP.:	IR 1:	TP 1:	#
DTP: d0 h0 m30 s0	DTA:	RESP.:	IR 2:	TP 2:	#
DTP: d0 h1 m0 s0	DTA:	RESP.:	IR 3:	TP 3:	#
DTP: d0 h1 m30 s0	DTA:	RESP.:	IR 4:	TP 4:	#
DTP: d0 h2 m0 s0	DTA:	RESP.:	IR 5:	TP 5:	#
DTP: d0 h3 m0 s0	DTA:	RESP.:	IR 6:	TP 6:	#
DTP: d0 h4 m0 s0	DTA:	RESP.:	IR 7:	TP 7:	#
DTP: d0 h6 m0 s0	DTA:	RESP.:	IR 8:	TP 8:	#
DTP: d0 h8 m0 s0	DTA:	RESP.:	IR 9:	TP 9:	#
DTP: d0 h12 m0 s0	DTA:	RESP.:	IR10:	TP10:	#
DTP: d1 h0 m0 s0	DTA:	RESP.:	IR11:	TP11:	#
DTP: d2 h0 m0 s0	DTA:	RESP.:	IR12:	TP12:	#
DTP: d3 h0 m0 s0	DTA:	RESP.:	IR13:	TP13:	#
DTP: d4 h0 m0 s0	DTA:	RESP.:	IR14:	TP14:	#
DTP: d5 h0 m0 s0	DTA:	RESP.:	IR15:	TP15:	#

DT: day&time P:planned A:analysis; RESP:responsible; IR:interim result; TP:testpoint result

DATASHEET PRINTED 29-Apr-92 17:03

THE VALIDITY OF RAW DATA IS CONFIRMED BY STUDY DIRECTOR:

DATE: SIGNATURE:

SYMBIOS DATASHEET (c)1986-1990 SYMBIOS I; CV: 920427.S31 STUDY-NUMBER: 91089;

TREATMENT: A SUBJECT-NUMBER: 1
ITEMNAME: DRUG ADMINISTRATION P.O.
ITEM: H001 INAME : DAPO
NORM RANGE: 0 - 1 SCORE INDEX

METHOD: 0: NOT ADMINISTERED; 1: ADMINISTERED

INITIAL EXAMINATION: FINAL EXAMINATION: COMMENTS:

DTP: d0 h0 m0 s0 DTA: RESP.: IR 1: TP 1: #

DT: day&time P:planned A:analysis; RESP:responsible; IR:interim result; TP:testpoint result

DATASHEET PRINTED 29-Apr-92 17:03

THE VALIDITY OF RAW DATA IS CONFIRMED BY STUDY DIRECTOR:

DATE: SIGNATURE:

Date: ; Page:

SYMBIOS - DATA SHEET FOR ADVERSE EVENTS (c) SYMBIOS 1991

Fill in "star-shaped" fields immediately! Use "TIME" - template for calculation of onset and duration!

STUDY NUMBER: 91089

Subject number in current study (SN)

Treatment under which event occurred
(if study is blind, enter blinded treatment code) (TREATMTGR; 1)

Reported event
(REPEVENT; 104)

Code according to standardized thesaurus (CODE; 11)

Term that is keyed by CODE
(CODETERM; 104)

Comment of study director
(COMMENT; 104)

Date and time of the event's onset:

Day	Month	Year	Hour	Minute

Day of event after study onset (ONSETDAY)

Hour of event at this day (ONSETHOUR)

Minute of event at this hour (ONSETMINUTE)

Date and time of the event's end:

Day	Month	Year	Hour	Minute

Duration (days) of event after beginning of the event (DURATIONDAYS)

Duration (hours) of event at the last duration-day (DURATIONHOURS)

Duration (minutes) of event at the last duration-hour (DURATIONMINUTES)

Date and time of the individual treatment onset (cf. RANDOMIZATION LIST)

Day	Month	Year	Hour	Minute

Maximum intensity of event
(1=mild, 2=moderate, 3=severe) (INTENSITY)

Relation to test-treatment
(1=none, 2=possible, 3=sure) (RELATION)

Date: Study Director: