

**ESTUDIO DE CONVERSION FARMACOCINETICA DE
EQUORAL® (IVAX-CR) Y NEORAL, EN ADULTOS
RECEPTORES DE TRANSPLANTE RENAL, ESTABILIZADOS**

53/EQ/01/PK

1. TITLE PAGE

CLINICAL STUDY REPORT

Study No. 53/EQ/01/PK

A Pharmacokinetic Conversion Study of Equoral® (IVAX-CR) and Neoral In Stable Adult Renal Transplant Recipients

Test drug/investigational product	Equoral® capsules
Design	Multi-centre, multinational, open-label, conversion study
Sponsor	IVAX Pharmaceuticals s.r.o. Ostravská 29, 747 70 Opava-Komárov, Czech Republic
Development phase	Phase I.
Study initiation date	September 4, 2002 (first subject enrolled)
Study completion date	November 4, 2003 (last subject completed) The study was completed according to the Protocol.
Principal investigator and affiliation	Prof. Marwan Masri, MD Immunology and Transplantation Rizk Hospital, P.O.Box 11-3288, Beirut, Lebanon
Sponsor's responsible medical officer	Assoc. prof. V. Kamarád, MD, DSc Research & Development IVAX Pharmaceuticals s.r.o., Ostravská 29, 747 70 Opava 9 Czech Republic
Sponsor signatory responsible for the study report and contact person	Mgr. O. Řehulková Research & Development IVAX Pharmaceuticals s.r.o., Ostravská 29, 747 70 Opava 9 Czech Republic Tel.: +420553642642, fax: +420553642649, mobile: +420602583352 e-mail: olga_rehulkova@ivax-cz.com
Date and state of report	May 21, 2004, final version

The study was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents.

The report was prepared in accordance with the guideline "Note for guidance on the structure and content of clinical study reports - CPMP/ICH/137/95". The recommended structure and numbering was taken over (almost) "verbatim" to facilitate reviews. Topics or headings, respectively, not relevant for this kind of trial were marked as "not applicable / n.a."

Confidentiality statement This report is proprietary to the sponsor. It may not be amended or used without the agreement of the sponsor.

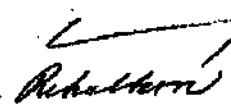
Equoral[®] capsules

Signature Page

The undersigned hereby confirm that the contents of this report accurately reflect the conduct and results of the study.

Author

24.5.2004



Date

Mgr. Olga Rehulková
Clinical Department of R&D
IVAX Pharmaceuticals s.r.o.
Opava-Komárov, CR

Statistician of Clinical Part of Study

4.6.2004



Date

Ing. Michael Rost
University of South Bohemia
Agriculture Faculty
České Budějovice, CR

Statistician of Pharmacokinetic Part of Study

24/5/04



Date

assoc. prof. František Perlík, MD, DSc
Pharmacological Institute of 1. LFUK
Prague-Albertov, CR

Sponsor's Responsible
Medical Officer

24.5.2004



Date

assoc. prof. Vojtěch Kamarád, MD, DSc
IVAX Pharmaceuticals s.r.o.
Opava-Komárov, CR

Equoral® capsules

2. SYNOPSIS

Name of sponsor/company: IVAX Pharmaceuticals s.r.o.	Individual study table referring to part of the dossier Not included in dossier	(For national authority use only)
Name of finished product: Equoral® capsules		
Name of active ingredient: Cyclosporine		
Title of the study:	A Pharmacokinetic Conversion Study of Equoral® (IVAX-CR) and Neoral In Stable Adult Renal Transplant Recipients Study number: 53/EQ/01/PK	
Principal investigator and study centre:	Prof. Marwan Masri, MD Immunology and Transplantation Rizk Hospital P.O.Box 11-3288, Beirut, Lebanon	
Other investigators and centres:	Prof. Gaby Kamel, MD Chairman Transplant Department Rizk Hospital P.O. Box 11-3288 Beirut, Lebanon Ali Hazalme, MD Ryak Hospital Beirut, Lebanon Prof. Mehmet Haberal Rector, Baskent University Director Transplantation Unit Cadde No: 77 Kat: 4 Bahcalievler Ankara 06490, Turkey Prof. Ahad J. Ghods, MD, FACP Hashemi Nejad Kidney Hospital Vanak Square 19386 Tehran - Iran	
Analytical centre:	Immunosynalytical Laboratory in each clinical centre with validated TDx Abbott monoclonal specific antibody methodology	
Publication:	Not planned yet	
Study period (years): date of first enrolment: September 4, 2002 date of last completed: November 4, 2003	Phase of development: phase I	
Objectives:	The primary objective of the study was to compare pharmacokinetics of the new generic cyclosporine formulation - Equoral® capsules after the switch from original formulation Neoral® capsules in stable adult renal transplant recipients. The secondary objective of the study was to evaluate C ₁ , C ₂ , BTL and changes in dosage of CyA. The tertiary objective of the study was to evaluate the safety of the switch from Sandimmun® Neoral capsules to Equoral® capsules.	
Primary endpoints:	Steady-state extent and rate parameters correlated for the dose (AUC _τ , Peak-trough-fluctuation, C _{min} -ss, C _{max} -ss) and their variabilities before and after the switch 1:1 (milligram: milligram) from Neoral capsules to Equoral capsules	

Equoral® capsules

Name of sponsor/company: IVAX Pharmaceuticals s.r.o.	Individual study table referring to part of the dossier Not included in dossier	(For national authority use only)
Name of finished product: Equoral® capsules		
Name of active ingredient: Cyclosporine		
Secondary endpoints:	C ₁ , C ₂ , BTL, oral daily dose of cyclosporine, number of dose adjustments	
Tertiary endpoints:	Vital signs, incidence of adverse events, changes in blood pressure, laboratory results.	
Methodology:	Stable renal transplant recipients ≥ 6 months post transplantation on Sandimmun® Neoral capsules BID therapy were screened in the pre-study period on the basis of inclusion and exclusion criteria. On the day -7, cyclosporine blood trough level was determined and samples for haematology, blood chemistry and urinalysis were collected. The patients, who fulfilled the inclusion and exclusion criteria, were enrolled in the study on the day 0, when he first sparse sampling PK (R) was performed. On the day 14, the 12-hour PK (R) was performed. On the day 15 in the morning, the patients were switched from Sandimmun® Neoral capsules BID to Equoral® capsules BID at an equivalent dosage (milligrams : milligrams). The second sparse sampling PK (I) was performed on the day 21. A 12-hour PK (I) was performed on the day 28. On the day 29 in the morning, the patients were switched from Equoral® capsules BID to Sandimmun® Neoral capsules BID at an equivalent dosage (mg : mg). Additional BTL were measured on days 18 and 35. In the afternoon before each 12-hour PK, the patients were hospitalized in the clinical unit until discharged after the 12-hour pharmacokinetic parts. During each pharmacokinetic part of study, 12 blood samples were taken. The doses of Equoral® or Sandimmun® Neoral were individualized to maintain whole blood trough levels of cyclosporine between 70-200 ng/mL (TDx Abbot). The samples for haematology, blood chemistry and urinalysis were also collected on the day 21. Safety parameters (vital signs, physical examinations, routine laboratory parameters, incidence of adverse events) were monitored at each visit.	
Sampling times for pharmacokinetics:	Pre-dose, 30 min, 1h, 1h 30 min, 2h, 3h, 4h, 5h, 6h, 8h, 10h and 12h	
Sparse sampling PK:	On days 0(R), 21(I)	
Additional BTL:	At screening, on day 18 and 35	
Number of patients:	Planned: 100 Enrolled: 70 Completed: 70	
Main criteria for inclusion:	• Either sex • Age: 18-70 years • First renal transplant (cadaveric or living donor) • No rejection episode in the past 6 months • Clinically stable for at least 6 months post transplantation with acceptable safety/tolerance to Sandimmun® Neoral capsules • Three last whole blood trough cyclosporine level in the range of 70-200 ng/ml • Stable serum creatinine in the past 3 months with no trend to increase	

Equoral[®] capsules

Name of sponsor/company: IVAX Pharmaceuticals s.r.o.	Individual study table referring to part of the dossier Not included in dossier	<i>(For national authority use only)</i>
Name of finished product: Equoral® capsules		
Name of active ingredient: Cyclosporine		
	• No hepatic dysfunction in the past 6 months (increase of aminotransferase <100% above the limit) • No history of alcohol or drug abuse or signs of alcohol-induced organ damage • No clinical symptoms of CMV infection in the past 6 months • No history or evidence of malignancy or any significant infection • Blood pressure in normotensive range with or without antihypertensive medication • Maintained on cyclosporine in double or triple combination with prednisone, azathioprine, mycophenolate mofetil • Doses of cyclosporine ≤ 8 mg/kg/day. The dose has to be stable over the previous 14 days prior to entry • Doses of concomitant medication stable 14 days prior to study entry	
Main criteria for exclusion:	• Significant hypersensitivity to cyclosporine or any related product or to castor oil, olive oil or corn oil • Pregnant or lactating females • Pre-menopausal woman of childbearing potential not using safe contraception • > 1 renal transplant or grafts of other organs (e.g. pancreas) • Uncontrolled blood pressure (resistant to antihypertensive therapy and despite reduction of cyclosporine dose) • History of chronic alcoholism, drug or narcotic abuse • History of myocardial infarction within 6 months of enrolment or uncontrolled cardiac arrhythmia • History of chronic alcoholism, drug or narcotic abuse • History of myocardial infarction within 6 months of enrolment or uncontrolled cardiac arrhythmia • Clinically relevant disease (including nervous system) or other abnormal condition which may compromise function of gastrointestinal tract, kidney or liver or which might influence cyclosporine pharmacokinetics • Exposition to any drug interfering with cyclosporine pharmacokinetics within 14 days prior to study entry • Exposition to any potentially nephrotoxic drug during 14 days prior to study entry • Patient with significant medical problem or unstable disease status	
Test product, dose and mode of administration, batch number:	Equoral® capsules (cyclosporine) 25 mg, 50 mg, 100 mg, IVAX Pharmaceuticals s.r.o., CR Packaging: 50 capsules in 1 package Dose: according to SPC, depends on whole blood trough levels of cyclosporine Mode of administration: oral Batch No: 5T111014 (25 mg), 5T111013 (50 mg), 5T111012 (100 mg)	

Equoral® capsules

Name of sponsor/company: IVAX Pharmaceuticals s.r.o.	Individual study table referring to part of the dossier	(For national authority use only)																				
Name of finished product: Equoral® capsules	Not included in dossier																					
Name of active ingredient: Cyclosporine																						
Reference product, dose and mode of administration, batch number:	Sandimmun® Neoral capsules (cyclosporine) 25 mg, 50 mg, 100 mg, Novartis Pharma AG, Switzerland Packaging: 50 capsules in 1 package Dose: according to SPC, depends on whole blood trough levels of cyclosporine Mode of administration: oral Batch No: 000MFD0601 (25 mg), 418MFD0601 (50 mg), F85MFD0701 (100 mg)																					
Duration of participation:	Screening: 1 week Study period I (taking Sandimmun® Neoral): 2 weeks Study period II (taking Equoral®): 2 weeks Study period III (taking Sandimmun® Neoral): 1 week																					
Pharmacokinetic evaluation:	Descriptive analysis for the pharmacokinetic parameters including mean, standard deviation, geometric mean, and 95% confidence intervals. After the log-data transformation, parametric (and non-parametric) statistical analysis with ANOVA model with patient, treatment-phase, and study centre as factors were performed. Additive model and non-parametric statistical analysis were used for analysis of T_{max} . The test/reference ratio of the parameters incl. their 90% confidence intervals were accepted using limit of 0.80, 1.25 (AUC, PTF) and 0.70, 1.43 (C_{max}), resp. C_1 and C_2 were analyzed using parametric t-test.																					
Safety evaluation:	Number of dose adjustments, daily doses of cyclosporine, adverse events, vital signs and physical examination findings were evaluated using elementary statistics. Adverse events were categorized and listed by study period Laboratory variables were calculated by non-parametric and parametric statistics.																					
Pharmacokinetic results:	Primary end-points <table><tr><th>Pharmacokinetic characteristic</th><th>Sandimmun® Neoral (R) Geometric mean exp(mean(ln) ± sd(ln))</th><th>Equoral® (T) Geometric mean exp(mean(ln) ± sd(ln))</th><th>T/R Geometric mean 90%-confidence interval</th></tr><tr><td>AUC₀₋₁₂ (ng/mL.h)</td><td>3638 (1738, 5314)</td><td>3108 (1621, 5304)</td><td>1.02 (0.89, 1.08)</td></tr><tr><td>C_{max} (ng/mL)</td><td>725 (461, 1138)</td><td>717 (445, 1147)</td><td>0.98 (0.82, 1.05)</td></tr><tr><td>C_{min} (ng/mL)</td><td>184 (68, 189)</td><td>107 (68, 205)</td><td>1.03 (0.98, 1.08)</td></tr><tr><td>PTP (%)</td><td>241 (173, 337)</td><td>228 (152, 345)</td><td>0.95 (0.80, 1.01)</td></tr></table> All these parameters are within given bioequivalence range.		Pharmacokinetic characteristic	Sandimmun® Neoral (R) Geometric mean exp(mean(ln) ± sd(ln))	Equoral® (T) Geometric mean exp(mean(ln) ± sd(ln))	T/R Geometric mean 90%-confidence interval	AUC ₀₋₁₂ (ng/mL.h)	3638 (1738, 5314)	3108 (1621, 5304)	1.02 (0.89, 1.08)	C_{max} (ng/mL)	725 (461, 1138)	717 (445, 1147)	0.98 (0.82, 1.05)	C_{min} (ng/mL)	184 (68, 189)	107 (68, 205)	1.03 (0.98, 1.08)	PTP (%)	241 (173, 337)	228 (152, 345)	0.95 (0.80, 1.01)
Pharmacokinetic characteristic	Sandimmun® Neoral (R) Geometric mean exp(mean(ln) ± sd(ln))	Equoral® (T) Geometric mean exp(mean(ln) ± sd(ln))	T/R Geometric mean 90%-confidence interval																			
AUC ₀₋₁₂ (ng/mL.h)	3638 (1738, 5314)	3108 (1621, 5304)	1.02 (0.89, 1.08)																			
C_{max} (ng/mL)	725 (461, 1138)	717 (445, 1147)	0.98 (0.82, 1.05)																			
C_{min} (ng/mL)	184 (68, 189)	107 (68, 205)	1.03 (0.98, 1.08)																			
PTP (%)	241 (173, 337)	228 (152, 345)	0.95 (0.80, 1.01)																			

Equoral® capsules

Name of sponsor/company: IVAX Pharmaceuticals s.r.o.	Individual study table referring to part of the dossier Not included in dossier	<i>(For national authority use only)</i>
Name of finished product: Equoral® capsules		
Name of active ingredient: Cyclosporine		
Pharmacokinetic results:	<u>Secondary end-points</u> <u>Blood trough levels</u> The differences between individual days are not statistically significant (Anova, F=0.02, p=0.98). <u>Cyclosporine concentrations (C₁, C₂)</u> In time point C ₁ , the mean cyclosporine concentration was 19 ng/mL (94-1602 ng/mL) and 401 ng/mL (49-1578 ng/mL) after Sandimmun® Neoral and Equoral®, respectively. The difference is statistically significant (t-test 2.28, p< 0.05). In time-point C ₂ , the mean cyclosporine concentration was 604 ng/mL (122-1808 ng/mL) and 591 ng/mL (85-1592 ng/mL) after Sandimmun® Neoral and Equoral®, respectively. The difference is not statistically significant.	
Safety results:	Patients were able to convert from Sandimmun® Neoral to Equoral® without the requirement of any dosage adjustment. The product Equoral® was well tolerated. No rejections and other serious adverse events occurred during the study. Monitoring of laboratory parameters, vital signs and physical findings gave no evidence for any clinically relevant effects caused by the study medication.	
Conclusions:	The pharmacokinetics of Equoral® is equivalent and indistinguishable from that of Sandimmun® Neoral. Equoral® is well tolerated and interchangeable with Sandimmun® Neoral in stable renal recipients.	
Date of report:	May 21, 2004	

Section 16

16. Appendices

- 16.1 Study Information
 - 16.1.1 Protocol and Protocol Amendments
 - 16.1.2 Sample Case Report Form (unique pages only)
 - 16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) – Representative Written Information for Patient and Sample Consent Form
 - 16.1.4 List and Description of Investigators and Other Important Participants in the Study, including Brief (1 page) CVs or Equivalent Summaries of Training and Experience relevant to the Performance of the Clinical Study
 - 16.1.5 Signature of Principal or Co-ordinating Investigator(s) or Sponsor's Responsible Medical Officer depending on the Regulatory Authority's Requirement
 - 16.1.6 Listing of Patients receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than One Batch was used
 - 16.1.7 Randomisation Scheme and Codes (Patient Identification and Treatment Assigned)
 - 16.1.8 Audit Certificates (if available)
 - 16.1.9 Documentation of Statistical Methods
 - 16.1.10 Documentation of Inter-laboratory Standardisation Methods and Quality assurance procedures if used
 - 16.1.11 Publications based on the Study
 - 16.1.12 Important Publications referenced in the Report
- 16.2 Subject Data Listings
 - 16.2.1 Discontinued Patients
 - 16.2.2 Protocol Deviations
 - 16.2.3 Patients excluded from Efficacy Analysis
 - 16.2.4 Demographic Data
 - 16.2.5 Compliance and/or Drug Concentration Data (if available)
 - 16.2.6 Individual Efficacy Response Data
 - 16.2.7 Adverse Event Listings (each patient)
 - 16.2.8 Listing of Individual Laboratory Measurements by Patient, when required by Regulatory Authorities
 - 16.2.9 Listing of Individual Vital Signs Measurements (by Patient)
- 16.3 Case Report Forms
 - 16.3.1 CRFs for Deaths, Other Serious Adverse Events and Withdrawals for AE
 - 16.3.2 Other CRFs submitted
- 16.4 Individual Patient Data Listings (US Archival Listings)

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALAT	alanine aminotransferase
ANOVA	Analysis of variance
ASAT	aspartate aminotransferase
ALP	alkaline phosphatase
AUC _τ	area under the concentration-time curve on steady-state dosing interval
BP	blood pressure
bpm	beats per minute
BTL	blood trough levels
CMV	cytomegalovirus
CRF	Case Report Form
CRO	Contract Research Organization
C _{max}	maximum cyclosporine blood concentration
C _{min}	minimum cyclosporine blood concentration
CyA	cyclosporine A
GCP	Good Clinical Practice
GMT	Glutaryl transpeptidase
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
mg	milligram
K _e	elimination rate constant
kg	kilogram(s)
min(s)	minute(s)
MRT	mean residence time
PK	pharmacokinetics
PTF	peak-through fluctuation
R	reference drug
RBC	red blood cell (count)
RIA	radioimmunoassay
RT	renal transplant
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
T	test product
t _{1/2}	half-life
T _{max}	time of maximum cyclosporine blood concentration
Tx	Transplantation
UV	Ultraviolet
WBC	white blood cell (count)

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The National Ethics Committees reviewed the protocol of the study. The investigators did not initiate the trial before the EC's written approval or favourable opinion of the protocol – including the patient's information and informed consent form – was obtained.

A copy of Ethics Committees' votes are given in SECTION 16.1.3.

5.2 Ethical Conduct of the Study

The study was conducted in full conformance with the ethical principles of World Medical Association Declaration of Helsinki 1964 (revised 1975, amended 1983, 1989, 1996 and WMA General Assembly, Edinburgh, Scotland, October 2000).

5.3 Subject Information and Consent

The principles of the informed consent in the current version of the Declaration of Helsinki were implemented for this study before protocol-specified procedures were carried out. The written consent document embodies the elements of an informed consent as described in the Declaration of Helsinki, the ICH-GCP Guidelines and complies with local regulations.

Patients who were asked to participate in clinical research were entitled to choose whether or not to take part. Their decision was voluntary and they should be competent to understand what was involved. Patients received adequate verbal and written information about the study which was in local language. The verbal explanation to the patient was either performed by the investigator or a medically qualified deputy who was a co-worker for the study. The verbal explanation covered all the elements specified in the written information provided for the patient. The investigator informed the patient of the aims, methods, anticipated benefits and potential risks of the study including any discomfort it may entail. The patient was given every opportunity to clarify any points the patient did not understand and if necessary ask for more information. At the end of the interview the patient might be given time to reflect, if this was appropriate. It should be emphasised that the patient was at liberty to withdraw his/her consent to participate at any time, without penalty

or loss of benefits to which the patient is otherwise entitled. The investigator was responsible for obtaining the patient's freely given consent. The written consent form provided to the patient was signed and dated by the patient as well as the investigator. The patient was given a copy of the document which included the name and phone number of the person to contact in case of an emergency. The consents are kept on file by the investigator for possible inspection, monitoring and audit by Regulatory Authorities and/or Sponsor professional persons. The signature confirmed the consent which was based on information that was understood.

Sample written information for patients and consent form are provided in SECTION 18.1.3.

5.4 Regulatory Aspects

The trial was carried out in accordance with the applicable legal and regulatory requirements, in particular with

- International Conference on Harmonisation Guidelines for "Good Clinical Practice": Consolidated Guidelines, 17.1.1997
- Good Clinical Practice for Studies on Medicinal Products in the European Community (CPMP) Guidelines

and in accordance with all relevant local legal laws including respective drug laws and

Standard Operating Procedures (SOP) of IVAX Pharmaceuticals s.r.o.

Prior to the beginning of the study, the written approvals of the local Regulatory Authorities were obtained.

Equoral® capsules

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigators and Other Functions

Principal

Investigator: Professor Marwan Masri, MD
Immunology and Transplantation
Rizk Hospital
P.O.Box 11-3288, Beirut, Lebanon

Other

Investigators: Professor Gaby Kamel, MD
Chairman Transplant Department
Rizk Hospital
P.O. Box 11-3288 Beirut, Lebanon

Ali Hazime, MD
Ryak Hospital
Beirut, Lebanon

Professor Mehmet Haberal, MD
Rector, Baskent University
Director Transplantation Unit
Cadde No: 77 Kat: 4 Bahcelievler Ankara 06490, Turkey

Professor Syed Adibul Rizvi, MD
Director
Sindh Institute of Urology and Transplantation (SIUT)
Dow medical collage and Civil Hospital
Karachi 74400, Pakistan

Clinical Trial Manager,

Author of Protocol, Eva Kopečná, MD
Monitor of SAE: Clinical Department of R & D
IVAX Pharmaceuticals s.r.o.
Ostravská 29
747 70 Opava 9
Czech Republic

Statistician of Clinical

Part of the Study: Michael Rost, Ing., PhD
University of South Bohemia, Agriculture Faculty
Studentská 13
370 05 České Budějovice
Czech Republic

Statistician of Pharmacokinetic

Part of the Study: Assoc. prof. František Perlík, MD, DSc
Pharmacological Institute of 1.LFUK
Prague - Albertov
Czech Republic

Equoral® capsules

Sponsor: IVAX Pharmaceuticals s.r.o.
Ostravská 29
747 70 Opava 9
Czech Republic

**Sponsor's
Responsible
Medical Officer:** Assoc. prof. Vojtěch Kamarád, MD, DSc
Clinical department of R&D
IVAX Pharmaceuticals s.r.o.
Ostravská 29
747 70 Opava 9
Czech Republic

**Clinical Study
Report Author:** Olga Řehulková, Mgr
Clinical Department of R&D
IVAX Pharmaceuticals s.r.o.
Ostravská 29
747 70 Opava 9
Czech Republic

6.2 Responsibilities

The sponsor was responsible for the following:

- preparation of the clinical study protocol, case report forms (CRFs), information for patients, informed consent form
- provision of study medication
- packaging and labelling of study medication
- provision of relevant product information (Investigator's brochure)
- insurance for patients
- preparation of the clinical study report.

The organization TransMed S.A.L. was responsible for the following:

- submission of study documentation to Regulatory Authority
- notification of health authorities about serious adverse events
- co-ordination of the study
- monitoring.

The Main investigators were responsible for the following:

- submission of study documentation to the Ethics Committee
- recruitment of patients
- obtaining of patient's informed consent
- performance of clinical part of study
- notification to sponsor and EC of serious adverse events.

7. INTRODUCTION

7.1 General Information

Cyclosporine is an important immunosuppressive agent used in organ transplants and immunoregulatory disorders. After introduction of cyclosporine in the early 1980s, cadaveric kidney graft survival improved by 15 to 20%. A particular advantage of cyclosporine therapy is that, unlike cytotoxic immunosuppressants (e.g., azathioprine), cyclosporine lacks clinically important myelosuppressive activity. The clinical advantages of cyclosporine resulted in widespread use after kidney, pancreas, liver, lung, and heart transplantation.

After oral administration of Sandimmun®, the absorption of cyclosporine is highly variable. Peak concentrations in blood or plasma are reached in 1 to 8 hour after administration, depending on the formulation and subject population. Sandimmun® Neoral, a microemulsion formulation of cyclosporine, demonstrates considerably reduced variability in cyclosporine pharmacokinetic parameters. Equoral® capsules - the new IVAX Pharmaceuticals galenic formulation of cyclosporine is a generic formulation of cyclosporine to Sandimmun® Neoral capsules. Bioequivalence of the both formulations was approved in healthy volunteers under fed and fasting conditions.

Although cyclosporine belongs to drugs with narrow therapeutic index and bearing in the mind the comparison of parameter's intrasubject variability appears to be a good indicator of switchability, the comparative, non-randomized, steady-state pharmacokinetic conversion study in stable adult renal allograft recipients was performed. Nevertheless, the aim of the study was to assess safety and feasibility of 1:1 conversion and to establish an appropriate procedure to switch subjects safely from Sandimmun® Neoral capsules to Equoral® capsules.

7.2 Rationale/Specific Guidelines

The CPMP note for guidance on "Good Clinical Practice" CPMP/ICH/135/95 was followed in the development of the protocol.

8. STUDY OBJECTIVES

The primary objective of the study was to compare pharmacokinetics of the new generic cyclosporine formulation - Equoral® capsules after the switch from original formulation Sandimmun® Neoral capsules in stable adult renal transplant recipients.

Equoral® capsules

The secondary objective of the study was to evaluate C_1 , C_2 , BTL and changes in dosage of cyclosporine.

The tertiary objective of the study was to evaluate the safety of the switch from Sandimmun® Neoral capsules to Equoral® capsules in stable adult renal transplant recipients.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-description

This was multi-centre, multinational, open-label, pharmacokinetic, three-period conversion study.

Procedures at study visit

Stable renal transplant recipients ≥ 6 months post transplantation on Sandimmun® Neoral® capsules BID therapy were screened in the pre-study period on the basis of inclusion and exclusion criteria. On the day -7, cyclosporine blood trough level was determined and samples for haematology, blood chemistry and urinalysis were collected. The patients who fulfilled the inclusion and exclusion criteria were enrolled in the study on the day 0, when the first sparse sampling PK (R) was performed. On the day 14, a 12-hour PK (R) was performed. On the day 15 in the morning, the patients were switched from Sandimmun® Neoral capsules BID to Equoral® capsules BID at an equivalent dosage (milligrams : milligrams). The second sparse sampling PK (T) was performed on the day 21. A 12-hour PK (T) was performed on the day 28. On the day 29 in the morning, the patients were switched from Equoral® capsules BID to Sandimmun® Neoral capsules BID at an equivalent dosage (mg:mg). Additional BTL were measured on days 18 and 35.

In the afternoon before each 12-hour PK, the patients were hospitalized in the clinical unit until discharged after the 12-hour pharmacokinetic parts. During each pharmacokinetic part of study, 12 blood samples were taken. The doses of Equoral® or Sandimmun® Neoral were individualized to maintain whole blood trough levels of cyclosporine between 70-200 ng/mL (TDx Abbot). The samples for haematology, blood chemistry and urinalysis were collected also on the day 21. Safety parameters were monitored at each visit. During the study, the safety parameters (vital signs, physical examinations, routine laboratory parameters, incidence of adverse events) were monitored according to the flow chart. All data collected on each patient enrolled in the study had to be noted in the individual CRF.

Equoral® capsules

Pharmacokinetic study**Hospitalization**

The patients were admitted and housed in the clinical facility on the day prior to each 12-hour PK part and stayed hospitalized until discharged 12 hours after drug administration. In case of any adverse event, necessary action was taken till the event subsided.

Administration

The drug was administered between 7 and 8 a.m in the clinical unit to the patients while in sitting posture. The administration was always done under medical supervision. The patients were instructed to engage in normal activity for the first 4 hours after drug administration, avoiding both vigorous exertion and complete rest. Capsules were swallowed whole and flushed down with 200 ml of water. The same production lot of water was used in each phase of the study.

Special dietary requirements

Standardized menu in each centre was served for both 12-hour PK periods.

Flow chart

Applicable to Treatment	Time relative to Drug Intake (oral dose)	Approx. Clock Time (h. min.)	Adverse Events	Sampling for 12-hour Pharmacokinetic Evaluation	Vital signs	Posture Upright	Hospitalized
N or E	0	08.00	DRUG ADMINISTRATION		X		
		08.10	STANDARDIZED BREAKFAST				
	30 min		X	X			
	1 h		X	X			
	1 h 30 min		X	X			
	2 h		X	X	X		
	3 h		X	X			
	4 h				X		
		12.30	STANDARDIZED LUNCH				
	5 h		X	X			
	6 h		X	X	X		
	8 h		X	X			
		17.30	STANDARDIZED DINNER		X		
	10 h		X	X			
	12 h		X	X	X		

Treatment N: Sandimmun® Neoral capsules (Novartis, Switzerland)
 Treatment E: Equoral® capsules (IVAX Pharmaceuticals)

Equoral[®] capsules

Due to the sensitivity of cyclosporine to ultraviolet light, samples were collected and processed under conditions which minimize their UV exposure. Whole blood samples (each sample approx. 1 mL) were collected at the times specified above. The clock time of all blood draws were recorded and reported for each patient. Any deviation from the sampling schedule was recorded in the patient's sampling time sheet. Sampling time sheets for all patients were included in the CRF. The total volume of blood withdrawn over 12-hours of pharmacokinetic analysis did not exceed 14 mL. The blood samples were collected in appropriately labelled Tapval[®] EDTA-containing tubes. The tubes were labelled with the study identification number and a code that corresponded to patient identifier and sampling time and period. Immediately after collection, the filled blood collection tubes were inverted gently and frozen at -20° C, and stored in a refrigerator with a regular temperature record.

Cyclosporine blood level monitoring and labeling of tubes

Each tube with CyA blood level determination was labelled separately in each clinical site according to the following schedule:

- *determination of BTL*

The whole blood was taken 5 minutes prior to dosing.

DETERMINATION OF BLOOD TROUGH LEVEL		
Sequence: Number of patient -- Sandimmun [®] Neoral capsules (N) -- Number of blood collection for BTL		
Visit 1	Visit 4	Visit 7
Day -7	Day 18	Day 35
1 st BTL	2 nd BTL	3 rd BTL
*N-1	*E-2	*N-3

* number of patient

- *pharmacokinetics*

A total of twelve 1 mL blood samples was collected during each 12-hour PK period. A total of three 1 mL blood samples was collected during each 2-hour sparse sampling PK period. The venous blood samples were withdrawn at the following times when the dosing of a patient took place at 8.00 a.m. Sampling schedule:

Equoral® capsules

PHARMACOKINETICS			
Sequence: Number of patient- Sandimmun® Neoral capsules (N) or Equoral® capsules (E)- Number of PK - Number of blood collection in PK			
Visit 2	Visit 3	Visit 5	Visit 6
Day 0	Day 14	Day 21	Day 28
C0, C1, C2 - Neoral	PK (12-hour) - Neoral	C0, C1, C2 - Equoral	PK (12-hour)- Equoral
*N-1PK-1	*N-2PK-1	*E-3PK-1	*E-4PK-1
*N-1PK-2	*N-2PK-2	*E-3PK-2	*E-4PK-2
*N-1PK-3	*N-2PK-3	*E-3PK-3	*E-4PK-3
	*N-2PK-4		*E-4PK-4
	*N-2PK-5		*E-4PK-5
	*N-2PK-6		*E-4PK-6
	*N-2PK-7		*E-4PK-7
	*N-2PK-8		*E-4PK-8
	*N-2PK-9		*E-4PK-8
	*N-2PK-10		*E-4PK-10
	*N-2PK-11		*E-4PK-11
	*N-2PK-12		*E-4PK-12

* number of patient

Analytical procedures

Cyclosporine through blood levels were analyzed by a validated TDx Abbott monoclonal specific antibody methodology in the local Immunoanalytical Laboratories of each particular centre. The intention to use any analytical method was consulted first with the CRO Manager of the analytical part (prior to its validation). Finally, the validation of the method had to be approved by the CRO Manager of the analytical part before any collection of samples started.

Detailed study flow chart is shown in SECTION 9.5.1.1.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The purpose of this pharmacokinetic study performed in stable renal transplant recipients was to evaluate interchangeability of Equoral® and Sandimmun® Neoral. The study was designed as multi-centre, multinational, open-label, three-period conversion study. Such design is appropriate to achieve the established study purpose.

9.3 Selection of Study Population

The inclusion/exclusion criteria aimed at the population of stable adult renal transplant recipients. The patients were recruited from the centres' databases.

9.3.1 Inclusion Criteria

To be eligible for the study, a patient had to fulfil the following criteria:

Equoral[®] capsules

1. Either sex
2. Age: 18-70 years
3. First renal transplant (cadaveric or living donor)
4. No rejection episode in the past 6 months
5. Clinically stable for at least 6 months post transplantation with acceptable safety/tolerance to Sandimmun[®] Neoral capsules
6. Three last whole blood cyclosporine trough levels in the range of 70- 200 ng/ml
7. Stable serum creatinine in the past 3 months with no trend to increase
8. No hepatic dysfunction in the past 6 months (increase of aminotransferase < 100% above the limit)
9. No history of alcohol or drug abuse or signs of alcohol-induced organ damage
10. No clinical symptoms of CMV infection in the past 6 months
11. No history or evidence of malignancy or any significant infection
12. Blood pressure in normotensive range with or without antihypertensive medication
13. Maintained on cyclosporine in double or triple combination with prednisone, azathioprine, mycophenolate mofetil
14. Doses of cyclosporine < 8 mg/kg/day. The dose had to be stable over the previous 14 days prior to entry
15. Doses of concomitant medication stable 14 days prior to study entry
16. Patient's ability to communicate well with the investigator
17. Written informed consent was obtained
18. Patient was not participated in another clinical trial within 28 days preceding this study

9.3.2 Exclusion Criteria

A patient who met any of the following criteria was excluded from the study:

1. Significant history of hypersensitivity to cyclosporine or any related products
2. Significant history of hypersensitivity to castor oil, olive oil or corn oil
3. Pregnancy or lactating females
4. Pre-menopausal woman of childbearing potential not using safe contraception
5. >1 renal transplant or grafts of other organs (e.g., pancreas)
6. Use of routine immunosuppressive therapy other than azathioprine, mycophenolate mofetil or prednisone

Equoral[®] capsules

7. Uncontrolled blood pressure (resistant to antihypertensive therapy and despite reduction of cyclosporine dose)
8. History of chronic alcoholism, drug or narcotic abuse
9. History of myocardial infarction within 6 months of enrolment or uncontrolled cardiac arrhythmia
10. Clinically relevant disease (including nervous system) or other abnormal condition which may compromise function of gastrointestinal tract, kidney or liver or which might influence cyclosporine pharmacokinetics.
11. Exposition to any drug interfering with cyclosporine pharmacokinetics 14 days prior to study entry
12. Exposition to any potentially nephrotoxic drug during two weeks prior to study entry
13. Patients with significant medical problems or unstable disease states.

9.3.3 Removal of Patients from Therapy or Assessment

In accordance with the Declaration of Helsinki, the patients had the right to withdraw from the study at any time for any reason without the obligation of explanation.

The investigator had the right to withdraw patients from the study in the case of serious adverse event, necessity to take any prohibited medication, protocol violations, withdrawal of consent, failure to return for schedule visit or other reason incompatible with the study Protocol and Good Clinical Practice principles, or in order to protect the patient's health or the integrity of the study. Continued participation of any patient who violated the protocol was decided by the Sponsor's Medical Contact. Patients who were not evaluable due to protocol violations that were within the control of the investigator were not considered as completed subjects. Patients who did not complete the study were not replaced. Patients who were withdrawn due to adverse events were classified as "completed" and were not replaced. If a patient decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal had to be made with an explanation of why the patient is withdrawing from the study. Each case of patient's withdrawal had to be recorded in the CRF.

Equoral® capsules

9.4. Treatments

9.4.1 Treatments Administered

Patients on stable Sandimmun® Neoral capsules therapy were switched to Equoral capsules at an equivalent dosage (milligrams:milligrams) on the day 15 in the morning and then re-switched at an equivalent dosage (milligrams:milligrams) on the day 29 in the morning. Individual dosage was adjusted according to whole blood cyclosporine trough levels to maintain them within therapeutic range 70-200 ng/mL.

The study medications were taken with any non-alcoholic beverages except of grapefruit juice.

9.4.2 Identity of Investigational Products

	Test product	Reference product
Trade/ internal name	Equoral® capsules	Sandimmun® Neoral capsules
INN (active agents)	cyclosporine	cyclosporine
Composition (single unit)	25 mg, 50 mg, 100 mg cyclosporine per 1 capsule	25 mg, 50 mg, 100 mg cyclosporine per 1 capsule
Galenic form	soft gelatine capsules	soft gelatine capsules
Packaging	50 capsules in 1 package	50 capsules in 1 package
Manufacturer	IVAX Pharmaceuticals s.r.o. Opava 9, Czech Republic	Novartis Pharma AG, Switzerland
Batch no.	5T111014 (25 mg) 5T111013 (50 mg) 5T111012 (100 mg)	600MFD0601 (25 mg) 416MFD0601 (50 mg) F05MFD0701 (100 mg)
Dosage used	according to SPC during study normal patient's morning dose before pharmacokinetic part	according to SPC during study normal patient's morning dose before pharmacokinetic part
Duration of treatment	14 days	21 days

9.4.3 Method of Assigning Subjects to Treatment Groups

Not applicable.

9.4.4 Selection of Doses in the Study

The dosage of Sandimmun® Neoral and Equoral® complied with the Summary of Product Characteristics. Before pharmacokinetic part of the study, patients were administered normal morning dose of cyclosporine product. No particular adverse drug reactions were expected.

Equoral® capsules

9.4.5 Selection and Timing of Dose for Each Subject

Patients were administered test or reference product twice daily in the dose according to SPC during each study period. Before blood draw for steady state pharmacokinetics, normal morning dose of the drug was given between 7:00 and 8:00 a.m. Capsules were swallowed whole and flushed down with 200 ml of water. The same production lot of water was used in period of the study.

For details see part 9.1.

9.4.6 Blinding

Not applicable.

9.4.7 Prior and Concomitant Therapy / Special Dietary Requirement**CONCOMITANT THERAPY**

If, for medical reasons any new medication was administered during the study, the investigator should record all pertinent information. Patients who required medication for other than concomitant disease (e.g. antihypertensives), had to be on the same daily requirements for at least 14 days prior to the study start. When agents were administered for medical reasons that are known to interfere with activity of cytochrome P-450, bile metabolism (eg. cholestyramine) or gastric emptying, additional trough blood cyclosporine levels were determined during period of concomitant therapy. If it was necessary, adjustments of cyclosporine were done to keep within the specified target blood levels. All dose adjustments were made only by the investigator or his/her designee. All concomitant medication was recorded in the CRF with drug generic name, the explicit indication(s) for the drug, international disease code, daily dose and dosing frequency, dates (start/stop) and time of administration.

SPECIAL DIETARY REQUIREMENTS

During housing a standardized menu was served for both PK periods. Information on the amount of meal consumed and the time taken for consuming was recorded in the appropriate clinical raw data sheets. The actual time of meal distributions was also recorded.

The consumption of alcohol or xanthine-containing beverages and food (chocolates, tea, coffee or cola drinks) were prohibited for 24 hours before dosing and throughout the period of sample collection. The consumption of grapefruits, grapefruit juice or

Equoral® capsules

grapefruit-containing beverages and food were prohibited for 3 days before dosing and throughout the duration of the pharmacokinetic study. Cigarettes and tobacco products were prohibited throughout their stay at the clinical facility. On the days of PK study, the patients fasted overnight for 10 hours prior to drug intake.

THERAPY OF REJECTION

Acute rejection had to be treated by 500 mg of methylprednisolone on the first day and 250 mg on days 2, 3 and 4. If rejection was still present, the investigator could continue with methylprednisolone or administer a rabbit antihuman thymocytes globulin preparation or other approved monoclonal antibodies. I

9.4.8 Treatment Compliance

Compliance was assessed by a count of returned study medication capsules and packaging materials at the scheduled clinic visits and on the basis of comparison the relationship between trough levels and dosage.

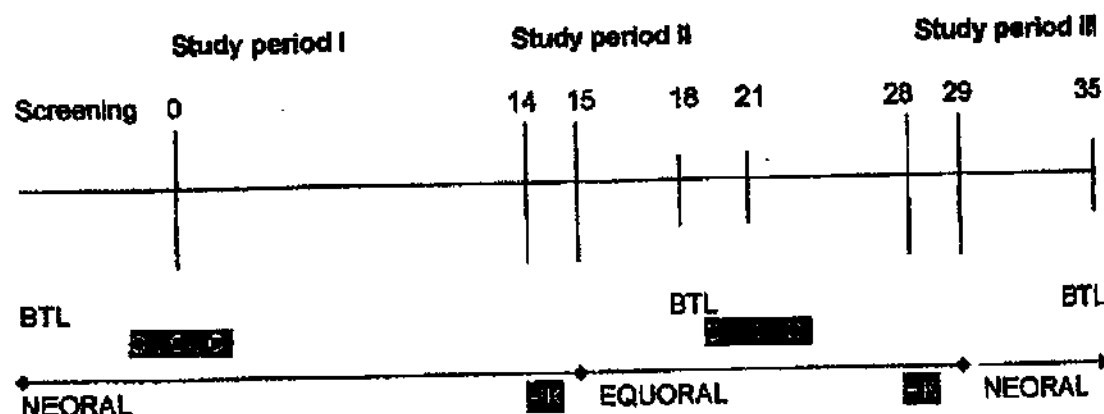
9.5 Pharmacokinetic and Safety Variables

9.5.1 Drug-Concentration and Safety Measurements Assessed and Flow Chart

9.5.1.1 Flow Chart

	Screening	Study period I			Study period II				Study period III		
Visit	1	2	3			4	5	6			7
Day	-7	0	13	14	15	18	21	27	28	29	35
General medical history	X										
Demographic data	X										
Physical examination, Vital signs	X	X	X			X	X	X			X
Informed consent	X										
Subject selection criteria	X										
Haematology Blood chemistry Urinalysis	X						X				
CyA blood trough level	X					X					X
Sparse samplings PK		X					X				
Pharmacokinetics			X					X			
Drug dispensing			At the discharge from hospital								
Adverse events assessment		X	X			X	X	X			X
Concomitant medication		X	X			X	X	X			X

Equoral® capsules

**9.5.1.2 Efficacy Measurements**

Efficacy was not assessed in the study.

9.5.1.3 Blood sampling

Blood for steady-state pharmacokinetics was taken prior to drug administration and at the following times after dosing: 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h. Blood for determination of blood trough level was taken 5 minutes prior to dosing on day -7, day 18 and day 35. Blood for 2-hour sparse sampling PK period was taken on day 0 and day 21.

For details see part 8.1.

9.5.1.4 Safety Measurements

Prior to the study, the patients were screened for eligibility. Screening was performed within 7 days prior to study period I. The following examinations were performed:

- demographic data
- detailed medical history and concomitant medication
- physical examination including assessment of vital signs (see below)
- clinical laboratory tests (haematology, blood chemistry, urinalysis) as detailed below.

Physical examination was as follows:

general appearance, skin, head, eyes/ears/nose/throat, neck, lymph nodes, breast (female), chest, lungs, heart, abdomen, extremities, musculoskeletal and neurological examination.

Vital signs: systolic and diastolic blood pressure, radial pulse rate, body weight and body temperature.

Blood pressure was measured once *always using the same arm* by a trained nurse with a mercury sphygmomanometer in the patients after they were sitting quietly for 5 minutes (method: Riva Rocci, Korotkoff V.). Radial pulse rate (after 5 minutes sitting) was measured manually by a trained nurse at the same time.

Clinical laboratory tests were composed of the following:

- Haematology
Haemoglobin, haematocrit, RBC, WBC with differential, platelets
- Blood chemistry
Creatinine, urea, uric acid, calcium, sodium, potassium, chloride, magnesium, inorganic phosphate, alkaline phosphatase (ALP), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), glutamic-pyruvate transaminase (GMT), total bilirubin, amylase, total protein, blood glucose, triglycerides, total cholesterol.
- Urinalysis
Protein, glucose, haemoglobin, bile (urobilinogen), acetone (ketone), amylase and pH.
- Pregnancy test (in pre-menopausal woman of childbearing potential).

The laboratory tests were performed in the laboratory of the respective clinic. Reference ranges for laboratory test results had to be provided by Main investigator of each investigational site prior to the study start. The investigators had to use the same clinical laboratory throughout the course of the study and notified to study monitor as soon as possible if normal laboratory test ranges changed at any time during the study. Blood samples were taken in fasting condition. In general, additional tests or repeat tests should be performed only if question arose, or following a protocol amendment, or if the laboratory results were aberrant and clinically relevant. It was the investigator's responsibility to document additional tests. Results of laboratory tests had to be properly recorded in CRF.

Physical examinations and vital signs measurements were repeated on day 0, 13, 14, 15, 18, 21, 27, 28, 29 and 35. Clinical laboratory tests (apart from pregnancy test) were repeated on day 21. Vital signs were also monitored if judged necessary by a physician in charge. If any clinically significant abnormalities occurred, measurements continued until the values returned to normal range.

Adverse events

Adverse events reported spontaneously and during interviews by the patients and adverse events observed by the investigator or his/her assistants were assessed throughout the entire study.

All adverse events, including observed, elicited, or volunteered problems, complaints or symptoms, were recorded in Adverse Event Section of CRF. The need to capture this information was not dependent upon whether adverse events were associated with the study medication. Adverse events resulting from concurrent illnesses, reactions to concurrent medications and progression of disease states were also recorded. In order to avoid vague, ambiguous or colloquial expressions, adverse events had to be recorded in standard medical terminology rather than the patient's own words. Symptoms were reported individually unless, in the judgment of the investigator, they were grouped under an inclusive term (e.g. flu-like symptoms). Each adverse event was evaluated for date/time of onset, duration, intensity, seriousness and causal relationship with study medication, outcome and other factors.

Specific rating scales for assessment of adverse event:

- Intensity

Mild: A reaction that followed a reasonable temporal sequence from administration of the investigatory study medication or in which transient, required no special treatment, and did not interfere with patient's daily activities.

Moderate: Introduced a low level of inconvenience or concern to the patient and might interfere with daily activities, but were usually ameliorated by simple therapeutic measures.

Severe: Interrupted a patient's usual daily activities and required systemic drug therapy or other treatment.

If the intensity of an adverse event changed more than once a day, the maximum severity for the event had to be recorded. In case the intensity category changed over a number of days, then these mini-events or changes should be recorded separately (i.e. having distinct onset dates).

Equoral® capsules

• Relationship to study medication

The causal relationship of the adverse event with study medication was defined according to Karch and Casagna.¹

Definite:	A reaction that followed a reasonable temporal sequence from administration of the investigatory study medication or in which the medication level has been established in body fluids or tissues, that followed a known or expected response pattern to the suspected investigatory study medication, and that was confirmed by improvement on stopping the dosage of the investigatory study medication, with reappearance of the reaction on repeated exposure (re-challenge).
Probable:	A reaction that followed a reasonable temporal sequence from administration of the investigatory study medication that followed a known or expected response pattern to the suspected investigatory study medication that was confirmed by stopping the dosage of the investigatory study medication, and that could not be reasonably explained by the known characteristics of the patient's clinical state.
Possible:	A reaction that followed a reasonable temporal sequence from administration of the investigatory study medication, that followed a known or expected response pattern to the suspected investigatory study medication, but that could readily have been produced by a number of other factors
Not Assessable:	A relationship for which no evaluation could be made.
None:	A reaction, for which sufficient information exists to indicate that the aetiology is unrelated to the investigatory study medication.

Serious adverse events

Any serious adverse event which occurred during the clinical trial, whether or not related to the study drug, had to be reported immediately (within 24 hours) by the investigator to the clinical trial monitor. The telephone report had to be followed by a full report to include copies of relevant hospital case records, autopsy reports and other documents where applicable. Those adverse events of a less serious nature had to be reported in writing in the study report.

Following-up adverse events

Investigator had to follow-up patients with adverse events until the event had subsided (disappeared) or until the condition had stabilized. Reports relative to the patient's subsequent course had to be submitted to the clinical trial monitor.

Overdose

Any instance of over-dosage (suspected or confirmed) had to be communicated to the sponsor within 24 hours and fully documented similarly to a serious adverse event. Details of any signs or symptoms and their management should be recorded including details.

Pregnancy

Patients who became pregnant during the study had to be discontinued the study immediately. Patients should be instructed to notify the investigator if, after completion of the study they became pregnant either during treatment phase of study:

- or within 30 days or five half-lives after the end of the treatment period, whichever was longer
- whenever possible a pregnancy should be followed to term, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.

All serious adverse events had to be recorded in the CRF.

9.5.2 Appropriateness of Measurements

Cyclosporine blood levels were measured by a validated TDx Abbott monoclonal specific antibody methodology, which is standard and widely used. Safety was assessed according to adverse events, physical examination inc. vital signs findings and results of clinical laboratory tests. The assessments were standard, widely used and generally recognised as reliable, accurate and relevant.

9.5.3 Primary Variables**Primary variables were as follows:**

- Area under the blood concentration/time curve over the steady-state dosing interval: AUC_t
- Maximum blood concentration in the dosing interval: C_{max-ss}

Equoral[®] capsules

- Minimum blood concentration in the dosing interval: C_{min-ss}
- Peak-trough-fluctuation: PTF.

9.5.4 Drug Concentration Measurements

Cyclosporine blood levels were measured by a validated TDx Abbott monoclonal specific antibody methodology in the local immunoanalytical Laboratories of each particular centre.

9.6 Data Quality Assurance**9.6.1 Study monitoring**

CRO TransMed S.A.L. maintained a close liaison with the investigator and staff to clarify problems that arose during the study and to insure that the investigation was carried out according to the Protocol. The study was monitored throughout by the responsible monitor in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and the progress of the study. The monitoring consisted of personal visits before the study was initiated, when the centre was opened, at appropriate intervals during the study and at the end of the study. The monitoring included also communications via telephone and letter.

The CRO TransMed S.A.L. was responsible according to ICH GCP guidelines for assuring proper study conduct as regards protocol adherence and validity of the data recorded on the CRF. The monitors of TransMed S.A.L. assisted the investigator in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, the monitors ensured that the investigator understood all applicable regulation concerning the clinical evaluation of an investigational drug, as laid down in ICH GCP guidelines.

The investigator agreed to allow the monitor access to the study drug dispensing and storage area and to all clinical data of the study patients for the above purposes and agreed to assist the monitor in these activities. The investigator accepted that the monitor visited the clinic at regular intervals to review and verify the data collected. The monitor regarded all information, which was supplied to him/her as strictly confidential. The monitoring visits were for the purpose of verifying adherence to the protocol and for completeness and exactness of data entered in the CRF and

Drug inventory forms. The monitor verified CRF entries by comparing them with the clinic/practice raw data, which made available for this purpose. The monitor retrieved complete CRF sections at each visit. Adequate time and space for these visits should be made available by the investigator.

9.6.2 Deviations from protocol

The investigator had to strictly adhere to the protocol approved by the Ethics Committee. All deviations from the protocol had to be reported to the Monitor. The continued participation of patients who are protocol violators was decided by the TransMed S.A.L. clinical trial manager. Patients who were not evaluable due to protocol violations that were within the control of the investigator were not considered as completed patients.

9.6.3 Discontinuation of the study

The study could be terminated at any time by TransMed S.A.L. (after agreement with sponsor) or by sponsor itself if serious or excessive significant side effects appeared; if the investigator did not adhere to the protocol; or if, in sponsor's opinion, there were no further benefits to be achieved from the study. In the event of such termination, the monitor had to inform the investigator and the appropriate Ethics Committee in writing of the reason for the discontinuation.

9.6.4 Quality assurance

This study might be subject to audit by sponsor or local and/or foreign Regulatory Authority. In such case, all relevant information should be available by the responsible investigator and he/she as well as the involved site personnel should be reserved time for review and discussions of any findings during the audit.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

STATISTICAL EVALUATION

Primary endpoints and other pharmacokinetic parameters

The primary variables (AUC_{0-24} , C_{max-ss} , C_{min-ss} , PTF) and other pharmacokinetic parameters were derived individually for each patient and each drug. The actual

Equoral® capsules

time of blood sampling was taken into consideration; the values below limit of quantification were not accepted for the next calculations. The following pharmacokinetic parameters of cyclosporine were analysed by model independent analysis:

- area under the blood concentration/time curve over one steady-state dosing interval: $AUC\tau$
- maximum and minimum blood concentration in the dosing interval: $C_{max,ss}$, $C_{min,ss}$ (taken directly from the blood concentration/time curve)
- peak-trough-fluctuation: $PTF = (C_{max,ss} - C_{min,ss}) / C_{min,ss}$, where $C_{min,ss} = AUC\tau / \tau$
- time point of maximum blood concentration: T_{max}
- terminal elimination rate constant: λ_z
- half-life of drug elimination during terminal phase: $t_{1/2\lambda_z} = \ln 2 / \lambda_z$
- mean residence time: $MRT = AUMC / AUC$
- relative bioavailability: $F_{rel} = \text{mean } AUC\tau \text{ test} / \text{mean } AUC\tau \text{ reference}$.

All extent data were corrected for the administered dose. The area under the blood concentration-time curve ($AUC\tau$) was calculated using linear trapezoidal rule. The elimination rate constant was estimated using log-linear least squares regression analysis of the terminal part of the blood concentration/time curve. All results – except T_{max} data – were given as mean, standard deviation, geometric mean and of 95%-confidence limits, corresponding to $\text{mean} \pm t_{\alpha/(n-1)} \cdot \text{SEM}$ in the logarithmically transformed domain, i.e. $\exp(\text{mean}[\ln] \pm t_{\alpha/(n-1)} \cdot \text{SEM}[\ln])$. Parameter T_{max} was presented as median and extreme data.

Secondary endpoints

Blood trough levels, C_1 and C_2 were separately evaluated.

Tertiary endpoints

The treatment group was described using summary statistics. Demographic characteristics at baseline, number of dose adjustments, daily doses of cyclosporine, incidence of adverse events, incidence and severity of cyclosporine side effects including nephrotoxicity episodes and changes in blood pressure were analysed using appropriate statistical tests. Adverse events were categorized and listed by study period. Laboratory variables were calculated by parametric and non-parametric statistics.

Equoral® capsules

ANALYTICAL PLAN

Non-compartmental pharmacokinetic analysis of whole blood cyclosporine concentration was performed by means of KINBES module (version 1.34) of the MW/PHARM software (version 3.20). Statistical calculations were performed using STATISTICA, version 6 (StatSoft, U.S.A.).

Based on the multiplicative model for both extent and rate characteristics, a natural logarithmic transformation of parameters AUC_t , PTF, C_{max} , and C_{min} prior to data analysis was performed. In the case of parametric statistical analysis, an analysis of variance (ANOVA) model including patient, treatment-phase, and study centre as factors was performed.

The following hypothesis were tested at the 5% significance level as consumer risk:
 H_0 : the test formulation is non-equivalent to the reference, i.e. the mean response μ_T of the test formulation differs by $\delta = (0.22 \text{ for } AUC; 0.36 \text{ for } C_{max})$ or more from the mean response μ_R to application of the reference: $|\mu_T - \mu_R| \geq \delta$;

H_1 : the test formulation is equivalent to the reference, i.e. the mean response μ_T to dosing of the test formulation differs by less than $\delta = 0.22$ from the mean response μ_R to dosing of the reference: $|\mu_T - \mu_R| < \delta$. Consistent with the two one-sided tests, the 90%-confidence intervals were calculated for each parameter.

The null-hypothesis H_0 were rejected and the equivalence between test and reference formulation were concluded, if the 90%-confidence interval for the difference ($\mu_T - \mu_R$) of means was included in the interval -0.22 to 0.22, i.e. the ratio of geometric means (test /reference) was included in the bioequivalence range from 0.80 to 1.25 (AUC_t , PTF, C_{min}). For highly variable parameter C_{max} (if its coefficient of variability exceed 30%), the acceptance limits could be widened by Boddy up to range of (0.70, 1.43). Power of the tests should be 80% or more.

9.7.2 Determination of Sample Size

If the study were a cross-over bioequivalence assessment, based on multiplicative statistical model and following assumptions:

- (i) the real relative bioavailability of the test product between 91 and 110%,
- (ii) the bioequivalence range between 0.8 and 1.25,

- (iii) the level of significance $\alpha=5\%$,
 - (iv) the intra-subject coefficient of variability CV + 20%,
 - (v) the usually required power of the statistical test $(1 - \beta) = 80\%$,
- the sample size necessary for concluding bioequivalence would be approximately 32 patients.

9.8 Changes in the Conduct of the Study or Planned Analyses

The study was conducted as planned and in accordance with Protocol.

10. STUDY PATIENTS

10.1 Disposition of Subjects

Seventy (70) stable adult renal transplant recipients (48 males, 22 females) in the age from 20 to 67 years (mean = 35.09) were enrolled in the study. Of them, 30 patients were of Asian race and 40 patients of Caucasian race. No patient was prematurely withdrawn from the study.

Patients were maintained on Sandimmun® Neoral in double combination with prednisone (2, 2.9%) or in triple combination with mycophenolate mofetil and prednisone (27, 38.6%) or azathioprine and prednisone (41, 58.6%). Of concomitantly administered medication other than immunosuppressives, drugs to treat hypertension were the most frequently used (41, 58.6%).

A list of concomitant medication is shown in table 18 (see SECTION 14.1.3.)

10.2 Protocol Deviations

The study was performed in compliance with the Protocol with exception of the following cases of deviations from inclusion criteria:

- 27 patients were not normotensive on day -7
- 24 patients had blood trough cyclosporine level out of given range (70-200 mg/mL, RIA specific) on day -7
- 2 patients had significantly increased liver enzymes on day -7.

For further details see SECTION 16.2.2.

11. PHARMACOKINETIC EVALUATION

11.1 Data Sets Analyzed

All analyses were based on the entire sample of 70 patients.

11.2 Demographic and Other Baseline Characteristics

Totally, 70 stable adult renal transplant recipients (48 males, 22 females) in the age from 20 to 67 years (mean = 35.09) were enrolled and completed the study. Of them, 30 patients were of Asian race and 40 patients of Caucasian race. Weight of the patients ranged from 41.1 to 126 kilograms (mean = 65.98) and heights varied from 155 to 182 cm (mean = 153.17). Sixty four (64) patients were non-smokers and 68 patients did not take any alcohol. As regards to concomitant illnesses apart from urological diseases, patients suffered from pollen allergy (1, 1.4%), hypertension (1, 1.4%), itching (1, 1.4%), warts (1, 1.4%), diabetes mellitus (2, 2.9%), hepatitis B virus (1, 1.4%) and situs inversus totalis (1, 1.4%). One (1) patient (1.4%), suffered from arthralgia in the past, 1 patient (1.4%) underwent cholecystectomy and 1 patient (1.4%) lower caesarean section. A summary of the demographic characteristics is shown in SECTION 14.1.

A tabular listing of demographic data by patients is shown in SECTION 16.2.4.

11.3 Measurements of Treatment Compliance

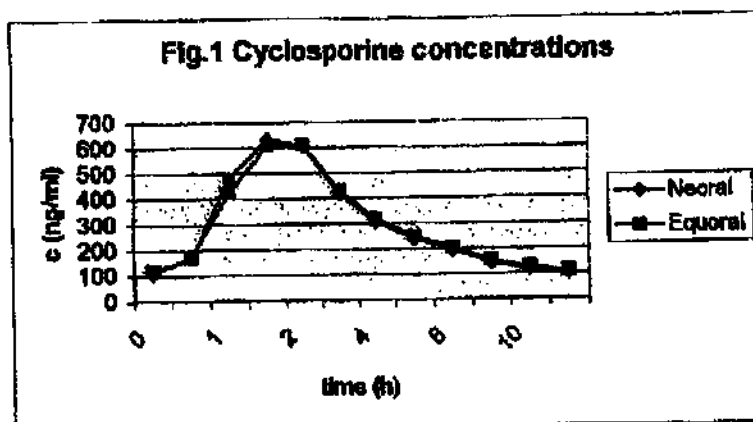
Treatment compliance was apparently good (cf. individual cyclosporine concentration/time data; see SECTION 14.2.1).

11.4 Pharmacokinetic Results and Tabulation of Individual Patient Data

11.4.1 Analysis of Pharmacokinetics

Cyclosporine concentrations

The course of mean cyclosporine concentrations (geometric mean) in time for both products is shown in Figure 1. In ascending part of the curve, in time interval after 1 and 1.5 hours, mean cyclosporine concentrations following administration of Sandimmun® Neoral were higher compared to those following Equoral®. In subsequent course, mean values of both curves are practically overlapped. Concentrations of cyclosporine by patient are listed in SECTION 14.2.1 and APPENDIX 16.2.5.



Elimination half-life

Elimination half-life was calculated from elimination constant calculated from individual values of time course of terminal elimination phase. The values of elimination half-life for Sandimmun® Neoral and Equoral® are summarized in table 21 (see SECTION 14.2.2). Geometric mean of $t_{1/2\alpha}$ for both products was practically the same (Sandimmun® Neoral 6.29 h, Equoral® 6.31 h). In elimination rate, high interindividual differences were found out in Sandimmun® Neoral (range 2.13-13.96 h) and Equoral® (range 3.10-12.12 h). However, intraindividual differences were not statistically significant (pair t-test $t=0.13$).

Evaluation of relative bioavailability

Evaluation of relative bioavailability judged various parameters characterizing rate and extent of relative bioavailability.

Primary endpoints

Individual values of primary pharmacokinetic parameters are summarized in following tables: AUC_t (table 22), C_{max} (table 23), C_{min} (table 24), PTF% (table 25) a MRT (table 26) (see SECTION 14.2.2). At first, the differences between centres were evaluated by ANOVA.

Source of variability	Sum of squares	Degree of freedom	Average square	F	Significance
AUC _t	inter	2	0.052	1.915	p > 0.05
	intra	87	0.027		
C _{max}	inter	2	0.038	0.421	p > 0.05
	intra	87	0.090		
C _{min}	inter	2	0.260	4.363	p < 0.05
	intra	87	0.059		

Equoral® capsules

PTF(%)	Inter	0.141	2	0.070	0.778	p > 0.05
	intra	6.060	67	0.090		

MRT	Inter	1.60	2	0.800	1.300	p > 0.05
	intra	41.20	67	0.061		

Analysis of variance of relative bioavailability (T/R) between particular centres showed statistically significant difference only in parameter C_{min} . These results enable overall analysis of all centres. During evaluation of relative availability, the following results (point estimate, 90% confidence interval) were obtained after change of products:

Pharmacokinetic characteristic	Sandimmun® Neoral (R) Geometric mean, n = 12 exp(mean(n) ± sd(n))	Equoral (T) Geometric mean, n = 12 exp(mean(n) ± sd(n))	T/R Geometric mean 90%-confidence interval
AUC _t (ng/mLh)	3039 (1738, 5314)	3108 (1821, 5304)	1.02 (0.99, 1.06)
C_{max} (ng/mL)	726 (461, 1139)	717 (449, 1147)	0.99 (0.93, 1.05)
C_{min} (ng/mL)	104 (56, 193)	107 (56, 205)	1.03 (0.98, 1.08)
PTF (%)	241 (173, 337)	229 (152, 345)	0.95 (0.90, 1.01)
MRT (h)	8.01 (5.47, 11.77)	8.40 (6.33, 11.15)	1.05 (0.89, 1.21)

Secondary endpointsBlood trough levels

The determination of blood trough cyclosporine levels was included in inclusion criteria (on day -7). This determination was repeated after switch to Equoral® (on day 18) and after re-switch to Sandimmun® Neoral (on day 35). The results are summarized in table 27 (see SECTION 14.2.3). The differences between individual days are not statistically significant (Anova, F=0.02, p=0.98).

Analysis of Variance BTL					
Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	217,038	2	108,519	0,02	0,9833
Within groups	1,3343926	207	6446,34		
Total (Corr.)	1,3346106	209			

The differences in rate to reach concentrations of both products were evaluated using parameter T_{max} and by determination of cyclosporine concentrations in absorption phase of the drug (C_1 , C_2).

Time of maximum blood cyclosporine concentration (T_{max})

The results of evaluation of this parameter are summarized in table 28 (see SECTION 14.2.3). Mean of T_{max} (median 1.5 h) was identical for both products.

Cyclosporine concentrations (C_1 , C_2)

The determination of cyclosporine concentrations in „sparse sampling“ was performed in the beginning of study period I (on day 0) and after the switch to Equoral® (on day 21). Individual results are summarized in table 29 (see SECTION 14.2.3). In time point C_1 , i.e. 1 hour following administration of cyclosporine, the mean cyclosporine concentration was 19 ng/mL (range 94-1802 ng/mL and 401 ng/mL (range 49-1578 ng/mL) after Sandimmun® Neoral and Equoral®, respectively. The difference was statistically significant (t-test 2.28, $p < 0.05$). In time-point C_2 , i.e. 2 hours following administration of cyclosporine, the mean cyclosporine concentration was 804 ng/mL (range 122-1808 ng/mL) and 591 ng/mL (range 85-1592 ng/mL) after Sandimmun® Neoral and Equoral®, respectively. The difference is not statistically significant. In time 0, the higher mean cyclosporine concentration was recorded during therapy with Sandimmun® Neoral - 123 ng/mL (range 20-447 ng/mL) compared to Equoral® - 114 ng/mL (range 13-387 ng/mL). The difference was statistically significant (t-test 2.058, $p < 0.05$).

11.4.2 Statistical Issues

Complete documentation of statistical methods is included in APPENDIX 16.1.9.

11.4.3 Tabulation of Individual Data

By-patient listing of individual pharmacokinetic data is given in SECTION 14.2.

11.4.4 Medicinal Product Dose, Medicinal Product Concentration, and Relationships to Response

Not assessed.

11.4.5 Drug-drug and Drug-disease Interactions

Neither apparent relationship between response and concomitant therapy nor between response and concurrent illness were found out.

Equoral® capsules

11.4.6 By-subject Displays

Not applicable.

11.4.7 Pharmacokinetic Conclusions

The pharmacokinetic analysis was focused on comparison of pharmacokinetic parameters of cyclosporine in 70 stable adult renal transplant recipients switched from Sandimmun® Neoral (reference product) to Equoral® (test product) at an equivalent dosage (mg:mg).

The relative extent of absorption was evaluated using primary pharmacokinetic parameter - area under the concentration-time curve on steady-state dosing interval. Time estimate for AUC_τ was 1.02 (90% confidence interval: 0.99 - 1.06). Rate of absorption was evaluated by parameter PTF. Perceptual (%) time estimate for PTF was 0.95 (90% confidence interval: 0.90 - 1.01). The other parameter characterizing absorption rate was maximum cyclosporine concentrations C_{max-ss}. Time estimate for C_{max-ss} was 1.03 (90% confidence interval: 0.98, 1.08). All these parameters were within given bioequivalence range 0.8-1.25. No statistically significant differences in other parameters, such as C_{min-ss}, T_{max} and alternative pharmacokinetic parameter used in therapeutic monitoring of cyclosporine - C₂, were found out.

From pharmacokinetic point of view and basing on analysis of cyclosporine concentrations, change of both products enables effective and safe therapy.

12. SAFETY EVALUATION**12.1 Extent of Exposure**

During the study, all patients were maintained on their usual stable dosage of twice-daily Sandimmun® Neoral for the screening period (1 week), period I (2 weeks) and period III (1 week). In study period II, patients were switched from Sandimmun® Neoral on a milligram-for-milligram basis to twice-daily Equoral®. Doses were individualized per patient to maintain therapeutic trough levels of cyclosporine. No dosage adjustments were required for any patient after the switch to Equoral®.

Results of summary statistics for cyclosporine dose are shown in SECTION 14.2.4.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

The study medications were well tolerated. Adverse events were reported in 18 patients (25.7%). Two patients (2.9%), 17 patients (24.3%) and 15 patients (21.4%) experienced adverse events in study period I (Sandimmun® Neoral), period II (Equoral®) and period III (Sandimmun® Neoral), respectively. No graft rejection was observed in the study. Of adverse events, oral candidosis (24.3%), gingival hypertrophy (1.4%), fever (1.4%), headache (1.4%), epistaxis (1.4%), red right eye (1.4%) and itching (1.4%) occurred. These adverse events were mostly mild or moderate (91.3%), only 2 events were severe (gingival hypertrophy, headache), and related to the study medication (87%) apart from fever, headache and epistaxis which were probably caused by co-existent disease according to the assessment of investigator. No adverse event was serious and in no case the therapy with cyclosporine product had to be prematurely discontinued due to adverse event. The most frequent event was oral candidosis (17 patients) which began to appear during therapy with Equoral® and continued after switch to Sandimmun® Neoral till the end of the study almost in all patients (16). All these cases were judge to be related to the study medication by investigator, however, 6 patients was examined to have signs of candidosis (white tongue) even in the beginning of the study, so the direct causal relationship to Equoral® is questionable in these patients. The incidence of this adverse event could be theoretically connected with enhanced immunosuppression, but neither monitoring of cyclosporine blood trough levels nor results of laboratory tests proved this presumption. Because oral candidosis was found out only in 1 investigational centre, the influence of the centre on occurrence of this event can not be omitted. Only two adverse events (gingival hypertrophy, fever) occurred in study period I, other events were observed in study period II, usually one week following the switch from Sandimmun® Neoral to Equoral®, and lasted till the end of the study in majority cases.

All adverse events for each patient are listed in SECTION 16.2.7.

12.2.2 Display of Adverse Events

Summary tables for adverse events are displayed in SECTION 14.3.1.

12.2.3 Analysis of Adverse Events

The overall frequency of all adverse events apart from oral candidosis was low (6.6% patients). The incidence of oral candidosis was relatively high (24.3%), but this event was observed only in patients from 1 investigational centre. In period I, two adverse events were reported, in period II 22 events occurred and in period III 18 adverse events were observed. During period I (patients were treated with Sandimmun® Neoral), gingival hypertrophy (1, 1.4%) and fever (1, 1.4%) appeared. Both events are comprehensively described below.

- In patient No. 14/1 severe gingival hypertrophy was found out at physical examination performed in screening period. This event continued during the whole period of the study and did not require any treatment or dose adjustment. It was judged as non-serious and probably related to the study medication.
- Patient No. 7/4 experienced moderate fever on study day 13. This event was not serious, lasted 1 day and spontaneously disappeared without necessity to take any medicine. It was connected with co-existent disease. Relationship to the study medication was "none" according to the investigator's assessment.

In period II, in which patients took Equoral®, oral candidosis (16, 22.9%), gingival hypertrophy (1, 1.4%), fever (1, 1.4%), headache (1, 1.4%), epistaxis (1, 1.4%), red right eye (1.4%) and itching (1.4%) occurred. All these events appeared in this period apart from gingival hypertrophy which was already examined in screening period.

- In patient No. 1/1 oral thrush of moderate intensity was recorded on study day 21. This event continued till the end of the study (day 35) and then disappeared without any medical intervention. The investigators assessed the event as non-serious and probably related to the study medication. Oral thrush appeared on the same study day, lasted for the same period of time and with same relationship to the study medication occurred also in patients No. 3/1, No. 5/1, No. 6/1, No. 9/1, No. 11/1, No. 13/1 No. 14/1 and 20/1. This event was moderate in these patients except of patient No. 20/1 who experienced mild oral thrush. In patients No. 8/1, No. 12/1, No. 15/1, No. 16/1 and No. 17/1 moderate thrush probably related to the study medication appeared on study day 18 and persisted up to day 35. The oral thrushes were not treated in any case. Despite all these cases were judged to be probably related to the study medication, 5 patients

Equoral® capsules

(No. 6/1, No. 8/1, No. 9/1, No. 15/1, No. 16/1) had the signs of oral candidosis (white tongue) already in the beginning of the study.

- In patient No. 7/1 moderate oral thrush occurred on day 21. It lasted 8 days (till day 28) and disappeared without any medication or adjustment of cyclosporine dose. The investigator assessed the event as probably related to the study drug, but white tongue was already found out in screening period.
- In patient No. 18/1 white tongue of mild intensity was observed. This event started on study day 18, lasted for 18 days (till day 35), was non-serious and did not require any therapy. It was judged by the investigator to be probably caused by study medication.
- The case of the patient with gingival hypertrophy (No. 14/1) is described in this section under events reported in study period I.
- Patient No. 9/1 complained about severe headache and mild epistaxis on study day 18. Both events spontaneously disappeared without any medical intervention. The events were judged as non-serious and caused by co-existent disease.
- Patient No. 6/1 suffered from mild itching (mainly at night) from day 25 to 29 and moderate red right eye from day 27 to day 29. Both events were non-serious and needn't to be treated. There was possible causal relationship between their incidence and study medication according to the investigator's judgement.

The adverse events occurred in period II were non-serious, mostly moderate and mild (90.5%) and related to the study medications (90.5%) apart from epistaxis and headache which were caused by co-existent disease. The most common adverse event was oral candidosis. This event always appeared during Equoral® therapy, however, a sign of oral candidosis (white tongue) was already observed in 5 patients (7.1%) during inspection of oral cavity in the beginning of the study. Candidosis persisted after switch to Sandimmun® Neoral in majority of cases (93.7%).

Oral thrush (15, 21.4%), gingival hypertrophy (1, 1.4%), red right eye (1, 1.4%) and itching (1, 1.4%) were recorded in period III. These adverse events already occurred in previous period of the study except for one case of oral thrush (see below).

- Patient No. 10/1 experienced moderate oral thrush on day 29. It lasted 7 days and disappeared without any medication or adjustment of cyclosporine dose. The investigator assessed the event as probably related to the study drug.

Equoral® capsules

12.2.4 Listing of Adverse Events

By-patients listings of adverse events are given in SECTION 16.2.7.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events**12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events**

There were no deaths, other serious adverse events or other significant adverse events.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable.

12.4 Clinical Laboratory Evaluation**12.4.1 Listing of Individual Laboratory Measurements by Patients and Each Abnormal Laboratory Value**

The tabular listings by patient of all safety-related laboratory parameters are presented in SECTION 16.2.8.

Summary statistics and frequency tables for all laboratory parameters can be found in SECTION 14.3.5.

12.4.2.1 Laboratory Values over Time

The abnormalities in haematological parameters after the switch from Sandimmun® Neoral to Equoral® (on day 21) were mostly mild, clinically insignificant (excepting one case of erythropenia), not related to the study medication and occurred particularly in those patients who had abnormal baseline values. The frequency of abnormal values on day 21 did not differ significantly from that on day -7 apart from

Equoral® capsules

abnormalities of basophils which were more frequent on day 21. The difference between day -7 and 21 was statistically but not clinically relevant. The most frequent abnormal values were found out in haematocrit (54.3% on day -7, 57.1% on day 21), haemoglobin (62.9% on day -7, 67.1% on day 21) and RBC (62.9% on day -7, 67.1% on day 21). The number of values lower and higher than lower and upper limit of reference range, respectively, was as follows:

- decrease in haemoglobin – 40 (57.1%) on day -7, 43 (61.4%) on day 21
- decreased haematocrit – 34 (48.6%) on day -7, 35 (50%) on day 21
- erythropenia – 33 (47.1%) on day -7, 37 (52.9%) on day 21
- erythrocytosis – 11 (15.7%) on day -7, 10 (14.3%) on day 21
- increase in haemoglobin – 4 (5.7%) on day -7, 4 (5.7%) on day 21
- increased haematocrit – 4 (5.7%) on day -7, 5 (7.1%) on day 21.

The abnormalities were recorded less frequently in eosinophils (37.1% on day -7 and 21) and lymphocytes (34.3% on day -7, 35.7% on day 21). Both decrease and increase in these parameters were found out with the following frequency:

- decrease in eosinophils – 22 (31.4%) on day -7, 23 (32.9%) on day 21
- decrease in lymphocytes – 23 (32.9%) on day -7, 22 (31.4%) on day 21
- increase in eosinophils – 4 (5.7%) on day -7, 3 (4.3%) on day 21
- increase in lymphocytes – 1 (1.4%) on day -7, 3 (4.3%) on day 21.

Rarely, abnormal values of neutrophils (8.6% on day -7, 10% on day 21), monocytes (5.7% on day -7, 8.6% on day 21), WBC (5.7% on day -7, 7.1% on day 21), basophils (5.7% on day 21) and platelets (4.3% on day -7, 8.6% on day 21) were found out. The numbers of particular abnormalities were as follows:

- increased neutrophils – 6 (8.6%) on day -7 and 21
- increased basophils – 4 (5.7%) on day 21
- increased monocytes – 4 (5.7%) on day -7, 5 (7.1%) on day 21
- leukocytosis – 2 (2.9%) on day -7, 1 (1.4%) on day 21
- leukocytopenia – 2 (2.9%) on day -7, 4 (5.7%) on day 21
- thrombocytopenia – 2 (2.9%) on day -7, 6 (8.6%) on day 21
- decreased neutrophils – 1 (1.4%) on day 21

Equoral® capsules

- thrombocytosis – 1 (1.4%) on day -7.

There was only one clinically significant abnormal value, i.e. erythropenia ($1.7 \times 10^{12}/L$) in patient No. 29/1, in the study.

Most laboratory haematological findings out of normal range were not clinically relevant apart from one case of erythropenia. Patient No. 29/1 had decreased value of RBC in screening period on day -7 ($1.7 \times 10^{12}/L$), which was above the normal range on day 21 ($5.6 \times 10^{12}/L$). Haemoglobin was above the normal range on both study days (13.6 g/dL). This finding was judged as clinically significant by the investigator.

The overall incidence of abnormalities in blood biochemistry after the switch from Sandimmun® Neoral to Equoral® (on day 21) was comparable with that occurred on day -7. The abnormalities were mostly mild or moderate, clinically irrelevant (apart from 3 cases of increased levels of liver enzymes) and were recorded in patients who had abnormal baseline values in majority of cases. The most frequent abnormalities were observed for creatinine (50% on day -7, 52.9% on day 21), uric acid (50% on day -7, 47.1% on day 21), chlorides (50% on day -7, 47.1% on day 21), amylase (42.9% on day -7, 41.4% on day 21), triglycerides (41.4% on day -7, 42.9% on day 21), total cholesterol (40% on day -7, 37.1% on day 21) and phosphorus (40% on day -7, 37.1% on day 21). The number of values lower and higher than lower and upper limit of reference range, respectively, was as follows:

- increased creatinine – 34 (48.6%) on day -7, 35 (50%) on day 21
- increased chlorides – 35 (50%) on day -7, 33 (47.1%) on day 21
- hyperuricemia – 32 (45.7%) on day -7 and 21
- increased amylase – 30 (42.9%) on day -7, 29 (41.4%) on day 21
- hypercholesterolemia – 27 (38.6%) on day -7, 26 (37.1%) on day 21
- hypertriglyceridemia – 26 (37.1%) on day -7, 29 (41.4%) on day 21
- decreased phosphorus – 19 (27.1%) on day -7, 20 (28.6%) on day 21
- increased phosphorus – 9 (12.9%) on day -7, 6 (8.6%) on day 21
- decreased triglycerides – 3 (4.3%) on day -7, 1 (1.4%) on day 21
- decreased amylase – 3 (4.3%) on day -7, 2 (2.9%) on day 21
- decreased creatinine – 1 (1.4%) on day -7, 2 (2.9%) on day 21

Equoral® capsules

- hypouricemia – 1 (1.4%) on day -7 and 21.

None of these abnormalities was clinically significant. The increase in creatinine was mostly mild and occurred particularly in those patients who had increased baseline value. The frequency of increased creatinine values was the same at the beginning of the study (on day -7) and after the switch to Equoral® (on day 21).

The frequency of abnormal values of other laboratory parameters was lower without significant differences before and after the switch from Sandimmun® Neoral to Equoral®. The following abnormalities were recorded:

- increased ASAT – 10 (14.3%) on day -7, 7 (10%) on day 21
- increased ALP – 10 (14.3%) on day -7, 8 (11.4%) on day 21
- hypercalcemia – 9 (12.9%) on day -7, 4 (5.7%) on day 21
- increased GMT – 8 (11.4%) on day -7, 11 (15.7%) on day 21
- increased ALAT – 8 (11.4%) on day -7, 10 (14.3%) on day 21
- increased urea – 8 (11.4%) on day -7, 9 (12.9%) on day 21
- hyperbilirubinemia – 7 (10%) on day -7, 11 (15.7%) on day 21
- hypermagnesemia – 7 (10%) on day -7, 2 (2.9%) on day 21
- hyperglycemia – 6 (8.6%) on day -7, 4 (5.7%) on day 21
- hyperkalemia – 5 (7.1%) on day -7 and 21
- hypokalemia – 5 (7.1%) on day -7, 6 (8.6%) on day 21
- hypoproteinemia – 4 (5.7%) on day -7, 7 (10%) on day 21
- hypoglycemia – 3 (4.3%) on day -7, 1 (1.4%) on day 21
- hypernatremia – 3 (4.3%) on day -7, 4 (5.7%) on day 21
- hyponatremia – 3 (4.3%) on day -7, 9 (12.9%) on day 21
- hyperproteinemia – 2 (2.9%) on day -7, 4 (5.7%) on day 21
- hypocalcemia – 2 (2.9%) on day -7, 3 (4.3%) on day 21
- decreased ALP – 2 (2.9%) on day -7, 4 (5.7%) on day 21
- decreased GMT – 1 (1.4%) on day -7 and 21
- decreased urea – 1 (1.4%) on day 21.

Equoral® capsules

These abnormalities were mostly clinically insignificant with exception of two cases of increased ALAT and one case of increased ASAT which were deemed by the investigators to be of clinical relevance.

Patient No. 8/4 had increased value of ALAT (309 U/L) on day 21, however, baseline value was also significantly increased (193 U/L). The blood levels of other liver enzymes were in normal range after the switch besides GMT which was higher than upper limit of normal. Baseline values of GMT and ASAT were slightly increased.

In patient No. 15/4, the increased values of ALAT (208 U/L) and ASAT (127 U/L) were measured after switch (on day 21), but these values were lower than those recorded on day -7. The blood level of ALP was within normal range at both measurements and GMT level was higher than upper limit of normal on day -7 and in normal range on day 21.

Urinalysis detected proteinuria in 9 patients (6 (8.5%) on day -7, 7 (10%) on day 21) and haemoglobinuria in 4 patients (1 (1.4%) on day -7, 4 (5.7%) on day 21), which were assessed by the investigator to be clinically insignificant. No other abnormal values were found out.

The overall incidence of abnormalities in measured laboratory parameters, including those commonly reported for cyclosporine, such as increased creatinine and urea, increase in liver enzymes, hyperlipidaemia etc., after switch from Sandimmun® Neoral to Equoral® (on day 21) did not significantly differ from that recorded at the beginning of the study (on day -7).

12.4.2.2 Individual Patient Changes

There were no clinically significant changes in individual laboratory parameters from baseline in the study.

Mean values of laboratory parameters detected no clinically relevant differences between the two measurements, including creatinine (day -7, 1.24 ± 0.28 mg/dL; day 21, 1.27 ± 0.3 mg/dL). Statistically significant difference was found out only in one laboratory parameter - platelets (day -7, $239.29 \times 10^9/L$; day 21, $227.84 \times 10^9/L$).

Equoral® capsules

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety**12.5.1 Blood Pressure and Heart Rate**

Evaluation of vital signs demonstrated that no significant changes from baseline occurred during the study for any of measured parameters.

Individual data listings for vital signs are presented in SECTION 16.2.9. Summary statistics for vital signs are displayed in SECTION 14.3.6.

12.5.2 Physical Findings

There were no clinically significant individual physical findings and no relevant changes of physical findings apart from higher incidence of oral thrush during Equoral® therapy compared to baseline. All cases of oral thrushes are described in detail in SECTION 12.2.

Individual data listings for physical findings are presented in SECTION 16.2.9. Summary statistics for physical findings are displayed in SECTION 14.3.7.

12.6 Safety Conclusions

Patients were able to convert from Sandimmun® Neoral to Equoral® without the requirement of any dosage adjustment.

The product Equoral® was well tolerated. The incidence of adverse events was low apart from oral thrush with higher frequency after switch from Sandimmun® Neoral to Equoral® compared to period before switch. No rejections and other serious adverse events occurred during the study.

Monitoring of laboratory parameters, vital signs and physical findings gave no evidence for any clinically relevant effects caused by the study medication.

13. DISCUSSION AND OVERALL CONCLUSIONS

The pharmacokinetics of Equoral® (AUC_t , PTF, $C_{max,ss}$, $C_{min,ss}$, $t_{1/2,ss}$, c_2) were indistinguishable from the corresponding values obtained after administration of Sandimmun® Neoral in 70 stable renal recipients when administered under standard

Equoral® capsules

condition. The two bioequivalent capsule formulations were interchangeable with respect to AUC_t , PTF and C_{max-ss} at steady state. There were no statistically significant differences in blood trough levels across the entire study regardless of the formulation administered and no need for dosage adjustment in any of transplant recipients after switch to Equoral®. Thus Equoral® and Sandimmun® Neoral formulations are interchangeable and bioequivalent.

Equoral® was well tolerated. No graft rejections occurred during the study. Across all study periods, adverse events were reported by less than 30% of patients. This overall incidence rate compares favourably with that from other short-term cyclosporine studies in which stable renal transplant patients were converted from Sandimmun® (cyclosporine) to Sandimmun® Neoral.^{2,3}

The most frequently reported adverse event in the study – infection (oral thrush) – is well known to be cyclosporine related. The higher incidence of this event after switch from Sandimmun® Neoral to Equoral® could be connected with enhanced immunosuppression according to the Investigator's assessment, but neither monitoring of cyclosporine blood trough levels nor results of laboratory tests proved this presumption. With the exception of one case of gingival hypertrophy, there were no reports of other common cyclosporine-related adverse events, such as hirsutism, tremor and renal dysfunction (indicated by increased serum creatinine levels). The finding of stable serum creatinine levels is consistent with previous cyclosporine conversion studies.^{4,5}

This study provides clinically relevant evidence of the safety profile of Equoral® and equivalence with Sandimmun® Neoral cyclosporine capsules. Patients were able to convert from Sandimmun® Neoral to Equoral® on a milligram-for-milligram basis without the requirement of any dosage adjustment. The study demonstrated that renal transplant recipients responded to Equoral® in the same manner in which they responded to Sandimmun® Neoral capsules.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

14.1.1 Disposition of patients

Table 1 Ratio of males and females according to race

Sex	Statistics	Asian	Caucasian	Row
Male	Count	20	28	48
	Column Percent	66.67%	70.00%	
	Row Percent	41.67%	58.33%	
	Total Percent	28.57%	40.00%	68.57%
Female	Count	10	12	22
	Column Percent	33.33%	30.00%	
	Row Percent	45.45%	54.55%	
	Total Percent	14.29%	17.14%	31.43%
All Groups	Count	30	40	70
	Total Percent	42.86%	57.14%	

Table 2 Demographic characteristics of males and females

Statistics:	Age (years)	Height (cm)	Weight (kg)
Valid N (missing)	66.00(2)	58.00(14)	69.00(1)
Mean	35.09	153.17	65.98
Median	33.50	163.00	66.80
Mode	29.00000	164.5920	61.00000
Frequency of mode	6.00	4.00	4.00
Minimum	20.00	55.00	41.10
Maximum	67.00	182.00	126.00
Lower quartile	29.00	158.72	57.00
Upper quartile	37.50	171.50	74.70
Range	47.00	127.00	84.90
Quartile range	8.50	14.78	17.70
Variance	65.84	1231.42	171.73
Standard Deviation	9.27	35.09	13.10

Table 3 Demographic characteristics of males

Statistics:	Age (years)	Height (cm)	Weight (kg)
Valid N (missing)	47(1)	38(10)	47(1)
Mean	35.277	152.240	68.436
Median	33.000	169.000	69.000
Mode	29.00000	Multiple	Multiple
Frequency of mode	5.000		
Minimum	20.000	55.000	42.100
Maximum	67.000	182.000	126.000
Lower quartile	29.000	158.000	58.000
Upper quartile	40.000	173.000	76.000
Range	47.000	127.000	83.900
Quartile range	11.000	15.000	18.000
Variance	98.857	1543.457	193.388
Standard Deviation	9.943	39.267	13.906

Equoral® capsules

Table 4 Demographic characteristics of females

Statistics:	Age (years)	Height (cm)	Weight (kg)
Valid N (missing)	21 (1)	18 (4)	22 (0)
Mean	34.667	155.132	60.732
Median	34.000	160.500	58.350
Mode	37.00000	Multiple	Multiple
Frequency of mode	5.000		
Minimum	25.000	58.000	41.100
Maximum	56.000	188.000	80.000
Lower quartile	29.000	155.448	55.500
Upper quartile	37.000	165.000	68.000
Range	31.000	110.000	38.900
Quartile range	8.000	9.552	12.500
Variance	59.933	618.631	90.094
Standard Deviation	7.742	24.872	9.492

Table 5 Ratio of particular races (males and females)

Race	Count	Cumulative	Percent	Cumulative %
Asian	30,00	30,00	42,86	42,86
Caucasian:	40,00	70,00	57,14	100,00
Missing	0,00	70,00	0,00	100,00

Table 6 Ratio of particular races (males)

	Count	Cumulative	Percent	Cumulative
Asian	20	20	41.66667	41.6667
Caucasian:	28	48	58.33333	100.0000
Missing	0	48	0.00000	100.0000

Table 7 Ratio of particular races (females)

	Count	Cumulative	Percent	Cumulative
Asian	10	10	45.45455	45.4545
Caucasian:	12	22	54.54545	100.0000
Missing	0	22	0.00000	100.0000

Equoral[®] capsules

14.1.2 Social history

Table 8 Ratio of smokers (males and females)

Smoking	Count	Cumulative	Percent	Cumulative %
No	64	64	91,43	91,43
Yes	8	70	8,57	100,00
Missing	0	70	0,00	100,00

Table 9 Ratio of smokers (males)

Smoking	Count	Cumulative	Percent	Cumulative
No	42	42	87,50000	87,50000
Yes	6	48	12,50000	100,00000
Missing	0	48	0,00000	100,00000

Table 10 Ratio of smokers (females):

Smoking	Count	Cumulative	Percent	Cumulative
No	22	22	100,0000	100,0000
Missing	0	22	0,0000	100,0000

Table 11 Ratio of smokers according to race (male)

Race	Statistics	No Smoking	Smoking	Row
Asian	Count	18	2	20
	Column Percent	42,86%	33,33%	
	Row Percent	90,00%	10,00%	
	Total Percent	37,50%	4,17%	41,67%
Caucasian	Count	24	4	28
	Column Percent	57,14%	66,67%	
	Row Percent	85,71%	14,29%	
	Total Percent	50,00%	8,33%	58,33%
All Groups	Count	42	6	48
	Total Percent	87,50%	12,50%	

Table 12 Ratio of patients taking alcohol (males and females)

Alcohol	Count	Cumulative	Percent	Cumulative %
No	68	68	97,14	97,14
Yes	1	69	1,43	98,57
Missing	1	70	1,43	100,00

Table 13 Ratio of patients taking alcohol (males)

Alcohol	Count	Cumulative	Percent	Cumulative
No	46	46	95,83333	95,83333
Yes	1	47	2,08333	97,9167
Missing	1	48	2,08333	100,0000

Table 14 Ratio of patients taking alcohol (females)

Alcohol	Count	Cumulative	Percent	Cumulative
No	22	22	100,0000	100,0000
Missing	0	22	0,0000	100,0000

Equoral[®] capsules

Table 15 Ratio of patients taking alcohol according to race (male)

Race	Statistics	No Alcohol	Alcohol	Row
Asian	Count	19	0	19
	Column Percent	41.30%	0.00%	
	Row Percent	100.00%	0.00%	
	Total Percent	40.43%	0.00%	40.43%
Caucasian	Count	27	1	28
	Column Percent	58.70%	100.00%	
	Row Percent	96.43%	3.57%	
	Total Percent	57.45%	2.13%	59.57%
All Groups	Count	46	1	47
	Total Percent	97.87%	2.13%	

14.1.3 General medical history

Table 16 Ratio of particular diseases

Disease Group	Diagnosis	No. of Patients	%	Still Present
Allergy	Pollen allergy	1	1.4	1
Cardiovascular	Hypertension	1	1.4	1
Dermatologic	Itching	1	1.4	1
	Warts	1	1.4	1
Endocrine	Diabetes mellitus	2	2.9	2
Gastrointestinal/hepatic	HBV	1	1.4	1
Musculoskeletal	Arthralgia (1994)	1	1.4	0
Major surgery	Cholecystectomy	1	1.4	0
	Lower caesarean section	1	1.4	0
Other	Situs inversus totalis	1	1.4	1

Table 17 Ratio of particular disease groups

Disease Group	Count	Cumulative count	Percent %	Cumulative %
Allergy	1	11	2.63	28.95
Cardiovascular	1	1	2.63	2.63
Dermatologic	2	7	5.26	18.42
Endocrine	2	10	5.26	28.32
Gastrointestinal/hepatic	1	5	2.63	13.16
Musculoskeletal	1	8	2.63	21.05
Major surgery	2	37	68.42	97.37
Other	1	38	2.63	100.00
Missing	0	38	0.00	100.00

Equoral[®] capsules

14.1.4 Concomitant medication

Table 18 List of concomitant medications

ATC		Number of patients
A02	Drugs for acid related disorders	
A02BA01	Cimetidine	10
A02BA03	Famotidine	8
A02BC01	Omeprazole	3
A10	Drugs used in diabetes	
A10AC01	Insulin (human)	4
A11	Vitamins	
A11AA03	Multivitamins and other minerals, incl. combinations	5
B03	Antianemic preparations	
B03AA07	Ferrous sulphate	1
B03AB02	Saccharated iron oxide	1
B03AE10	Iron in other combinations	4
B03BB01	Folic acid	3
C02	Antihypertensives	
C02CA04	Doxazosin	3
C03	Diuretics	
C03EA01	Hydrochlorothiazide and potassium-sparing agents	1
C07	Beta blocking agents	
C07AB03	Atenolol	8
C08	Calcium channel blockers	
C08CA01	Amlodipine	12
C08CA03	Isradipine	3
C08CA05	Nifedipine	1
C08DA01	Verapamil	1
C08DB01	Diltiazem	1
C09	Agents acting on the Renin-Angiotensin System	
C09AA01	Captopril	1
C09AA02	Enalapril	3
C09AA05	Ramipril	1
C09AA08	Quinapril	2
C09AA08	Cilazapril	2
C09AA10	Trandolapril	1
C09CA01	Losartan	1
C09CA03	Valsartan	2
C10	Serum lipid reducing agents	
C10AA01	Simvastatin	9
C10AA05	Atorvastatin	1
D01	Antifungals for dermatological use	
D01AA01	Nystatin	7
H02	Corticosteroids for systemic use	
H02AB07	Prednisone	70
J01	Antibacterials for systemic use	
J01EE01	Sulfamethoxazole and trimethoprim	9
L04	Immunosuppressive agents	
L04AA06	Mycophenolic acid	27
L04AX01	Azathioprine	41
M04	Antigout preparations	
M04AC01	Colchicine	1
N02	Analgesics	
N02BA01	Acetylsalicylic acid	1
N03	Antiepileptics	
N03AB02	Phenytoin	1

Equoral[®] capsules

ATC	Generic name of immunosuppressant	Number of patients
L04AA01 H02AB07	Cyclosporine + prednisone	2
L04AA01 H02AB07 L04AA06	Cyclosporine + prednisone + mycophenolic acid	27
L04AA01 H02AB07 L04AX01	Cyclosporine + prednisone + azathioprine	41

Equoral[®] capsules

14.2 Pharmacokinetic Data

14.2.1 Serum cyclosporine concentrations

Equoral® capsules

Table 19 Serum cyclosporine concentrations (ng/ml) Equoral

S. No.	C. No.	Through	Time (h)										
			0.5	1.00	1.5	2	3	4	5	6	8	10	12
1	3	147	242	532	628	791	631	578	238	209	132	152	180
2	3	187	423	768	620	529	488	805	418	280	228	217	169
3	3	118	277	741	1241	1058	498	315	349	259	178	176	144
4	3	178	200	1099	748	883	624	354	489	375	273	210	188
5	3	186	192	795	908	916	623	382	271	176	145	126	116
6	3	288	1179	931	598	404	320	295	239	198	160	138	148
7	3	164	153	280	748	903	683	902	398	319	219	168	134
8	3	186	179	282	828	1006	728	532	385	308	225	182	176
9	3	186	178	272	786	912	725	516	367	342	261	197	178
10	3	249	199	682	975	1091	660	586	425	328	225	191	158
1	4	125	125	190	548	884	522	377	236	198	151	105	81
2	4	141	143	370	808	824	558	365	252	230	198	141	134
3	4	111	103	404	916	728	518	350	262	202	122	97	91
4	4	446	407	378	387	748	814	564	498	488	356	320	326
5	4	80	806	1048	774	442	380	282	253	218	126	103	103
6	4	340	279	810	916	912	592	580	394	341	243	248	262
7	4	452	375	328	462	716	754	828	613	529	377	288	376
8	4	268	208	222	366	944	1008	762	534	394	280	270	242
9	4	219	188	284	1082	1354	1172	762	462	354	268	215	178
10	4	219	515	1280	1064	986	682	375	348	294	247	203	152
11	4	153	185	744	702	520	338	213	197	148	113	89	98
12	4	201	180	201	304	487	607	409	383	314	202	134	119
13	4	205	176	192	295	308	261	241	220	146	142	111	81
14	4	112	80	83	192	130	156	236	187	178	162	116	75
15	4	200	188	523	587	674	453	385	332	278	233	188	164
16	4	78	88	138	248	228	252	189	147	127	117	86	71
17	4	120	380	995	778	770	436	307	248	188	121	99	96
18	4	65	59	359	633	688	430	274	178	119	93	72	60
19	4	200	178	209	328	349	443	485	344	329	244	181	178
20	4	132	174	457	608	636	525	353	261	257	189	130	113
1	1	131	143	366	832	816	416	286	240	186	142	132	107
2	1	149	328	860	948	716	452	381	241	215	187	153	120
3	1	31	30	214	283	242	152	100	71	60	45	35	22
4	1	46	65	407	457	341	133	93	75	81	60	54	39
5	1	28	238	560	507	352	200	120	89	82	65	49	48
6	1	19	20	181	210	172	83	60	45	33	28	23	23
7	1	98	459	751	609	423	257	183	154	126	112	100	97
8	1	24	28	104	358	277	145	80	74	52	33	30	18
9	1	81	74	89	694	1241	653	360	319	207	175	118	98
10	1	84	107	338	830	751	387	232	179	155	87	75	70
11	1	32	33	186	460	337	148	94	73	59	44	29	28
12	1	144	181	153	346	683	625	384	289	274	194	159	155
13	1	47	71	443	632	634	294	167	131	108	79	61	54
14	1	187	328	605	972	959	478	389	278	222	174	180	160
15	1	18	15	120	189	147	72	37	32	27	20	22	22
16	1	46	44	144	472	583	295	180	112	98	73	75	57
17	1	78	164	568	703	702	427	289	190	159	109	84	81
18	1	91	200	688	792	821	393	275	210	162	126	88	83
19	1	141	176	729	874	781	438	381	288	248	172	141	135
20	1	128	231	816	899	792	493	433	375	237	261	183	144
21	1	249	308	940	1105	879	625	580	472	399	302	267	230
22	1	161	271	717	716	722	587	544	421	452	296	243	149

Table 19 Serum cyclosporine concentrations (ng/ml) Equoral
Time (h)

S. No.	C. No.	Through	0,5	1,00	1,5	2	3	4	5	6	8	10	12
23	1	117	232	639	693	514	478	400	318	284	206	159	98
24	1	139	302	566	968	944	480	390	364	299	219	165	140
25	1	156	219	987	1120	962	789	542	410	321	213	141	160
26	1	133	160	670	770	790	606	431	377	290	208	187	151
27	1	88	190	693	701	612	411	384	315	207	145	103	67
28	1	103	159	341	449	834	503	373	240	173	137	121	99
29	1	56	271	472	579	539	375	249	156	148	80	37	41
30	1	49	129	906	1109	644	351	173	141	117	79	52	89
31	1	293	509	1371	993	910	498	415	371	291	250	237	189
32	1	119	112	237	612	505	348	236	177	150	123	113	105
33	1	139	132	374	514	667	667	461	391	294	206	130	133
34	1	194	188	647	1196	1072	714	491	415	337	265	231	215
35	1	390	584	1327	1196	1141	981	692	667	483	423	400	354
36	1	113	204	388	588	661	421	354	211	201	169	163	128
37	1	192	215	511	661	532	471	409	364	306	269	215	174
38	1	245	303	632	1003	963	873	683	513	465	411	329	291
39	1	97	132	240	419	462	325	309	278	229	175	147	109
40	1	88	107	143	192	344	310	263	210	157	98	101	83
n		70	70	70	70	70	70	70	70	70	70	70	70
Geom. Mean		119,98	170,50	425,21	808,37	813,92	429,32	316,02	249,00	203,16	152,35	124,34	100,47
Exp (mean $\pm$ SC		58,89	76,90	209,94	386,35	373,42	247,07	172,64	136,47	110,65	81,30	66,09	56,43
Ln-data)		244,44	378,02	881,23	1010,25	1009,33	746,00	577,83	454,34	373,00	285,49	233,95	208,53
Median		135,5	186,5	464,5	647,0	690,5	478,0	363,0	274,5	220,0	173,0	139,5	119,5
Min.		15	15	89	102	130	72	37	32	27	20	22	18
Max.		452	1179	1371	1241	1354	1172	828	613	529	423	400	376

Equoral® capsules

Table 20 Serum cyclosporine concentrations (ng/ml) Neoral

			Time (h)										
S. No.	C. No.	Through	0.5	1	1.5	2	3	4	5	6	8	10	12
1	3	147	134	221	511	625	663	428	277	241	188	144	139
2	3	209	193	424	785	1067	742	690	359	303	220	197	167
3	3	174	174	261	784	1069	841	542	277	304	200	225	168
4	3	209	338	1157	473	774	562	397	333	268	211	198	174
5	3	201	188	807	1019	939	512	338	261	180	140	119	105
6	3	207	195	522	713	1028	998	698	481	446	308	284	206
7	3	143	214	679	950	1052	823	530	342	242	196	142	121
8	3	152	228	685	948	1104	534	588	308	262	188	162	146
9	3	185	236	729	985	1091	846	626	381	232	188	179	166
10	3	185	226	728	1106	872	532	364	271	199	158	147	132
1	4	141	97	356	582	454	478	408	292	221	146	100	98
2	4	121	142	824	908	858	384	238	220	198	178	150	127
3	4	110	140	588	782	868	428	288	262	213	126	100	89
4	4	371	382	490	1032	1586	1298	1134	754	694	454	373	344
5	4	82	264	1116	752	848	414	282	300	221	138	112	101
6	4	275	252	266	348	830	724	494	457	346	241	238	196
7	4	114	283	822	1238	1148	930	610	543	405	352	289	248
8	4	180	203	354	752	1030	688	428	363	304	187	156	151
9	4	288	289	838	1058	1052	592	486	374	329	192	141	137
10	4	241	519	1196	1084	838	594	397	358	339	226	204	190
11	4	97	98	180	486	382	258	170	145	126	83	78	55
12	4	368	232	620	912	744	562	447	376	323	279	185	178
13	4	167	134	184	452	540	424	265	227	170	123	100	79
14	4	105	84	76	280	452	420	307	198	188	97	73	74
15	4	184	334	854	898	628	511	374	278	258	189	149	168
16	4	77	62	117	179	188	186	118	96	131	84	78	57
17	4	107	270	482	533	434	354	284	213	167	108	95	70
18	4	47	148	436	388	346	437	170	138	117	81	49	31
19	4	185	275	498	541	527	435	388	278	221	181	180	140
20	4	104	138	229	334	399	242	381	286	236	152	113	90
1	1	135	288	898	967	759	457	328	285	238	188	168	168
2	1	132	251	721	858	787	378	113	232	193	96	122	149
3	1	34	46	133	295	283	183	332	88	70	26	35	32
4	1	31	48	525	557	385	178	100	84	68	66	48	48
5	1	39	46	954	608	534	184	118	112	79	52	48	41
6	1	10	215	239	189	96	67	36	35	22	8	16	11
7	1	68	235	803	551	395	173	148	135	106	67	65	60
8	1	16	34	296	300	196	98	85	42	37	24	28	21
9	1	78	89	498	687	608	352	338	279	125	157	122	85
10	1	50	53	241	683	751	340	181	147	107	78	54	60
11	1	28	24	127	401	371	148	81	61	61	39	18	25
12	1	163	187	594	1050	842	521	380	298	253	215	136	154
13	1	44	92	605	898	468	221	161	145	105	72	60	57
14	1	157	189	665	1231	995	565	359	282	238	183	187	141
15	1	5	41	208	171	113	64	42	27	30	20	7	14
16	1	47	62	418	482	468	180	133	102	84	65	51	81
17	1	73	225	808	818	665	374	282	205	183	118	89	89
18	1	83	210	635	709	598	380	242	200	184	112	108	93
19	1	124	168	781	883	723	451	365	254	223	161	120	109
20	1	133	210	890	789	715	466	418	322	276	290	218	154
21	1	237	282	986	1073	830	659	573	447	391	319	290	265
22	1	159	265	713	789	702	532	511	458	434	279	223	176

Equoral® capsules

Table 20 Serum cyclosporine concentrations (ng/ml) Neoral
Time (h)

S. No.	C. No.	Through	0,5	1	1,5	2	3	4	5	6	8	10	12
23	1	110	217	657	711	553	459	348	321	278	197	134	101
24	1	145	300	578	1000	831	465	402	400	310	203	166	152
25	1	177	221	845	990	834	731	402	400	351	243	188	180
26	1	120	212	700	710	690	847	429	312	290	187	132	140
27	1	71	107	630	640	555	399	354	301	239	146	89	55
28	1	106	178	356	413	785	450	384	286	248	166	142	113
29	1	48	243	465	513	526	439	300	210	153	89	42	39
30	1	78	148	666	654	713	218	194	168	101	84	77	52
31	1	254	295	526	634	794	696	570	411	365	265	264	238
32	1	94	296	538	506	390	308	275	202	190	144	70	94
33	1	101	264	784	725	533	352	250	189	147	145	110	88
34	1	169	178	257	302	505	649	740	486	318	257	222	194
35	1	324	800	1351	1373	1225	915	858	530	474	386	416	332
36	1	114	188	378	580	640	426	369	221	190	267	154	109
37	1	178	204	518	679	573	498	425	369	331	283	232	203
38	1	239	311	643	1119	1170	897	671	536	493	401	343	258
39	1	101	139	231	455	488	356	318	283	231	199	145	122
40	1	71	109	165	301	376	315	269	227	187	150	106	89
n		70	70	70	70	70	70	70	70	70	70	70	70
Geom. Mean		108,34	188,19	479,45	833,66	610,51	418,63	305,86	238,11	195,67	141,32	114,83	102,20
Exp (mean +/- S		49,54	87,25	268,31	390,42	363,39	228,24	159,06	125,88	103,31	68,11	54,47	50,64
Un-data)		238,90	324,23	896,87	1028,43	1025,72	787,83	588,19	450,36	370,62	283,21	242,48	206,25
Median		122,5	203	538	696	646	450	359	278	223	186	134	113
Min		5	0,5	1	1,5	2	3	4	5	6	6	7	11
Max		371	800	1351	1373	1586	1296	1134	754	594	454	418	344

Equoral[®] capsules

14.2.2 Individual listing of pharmacokinetic parameters

Table 21 Elimination characteristic: $t_{1/2}$ (h)

S. No.	C. No.	Neoral /R/	Equoral /T/
1	3	7,16	12,12
2	3	7,31	7,31
3	3	7,51	5,97
4	3	10,20	5,12
5	3	7,79	9,97
6	3	5,61	10,09
7	3	5,77	4,68
8	3	7,44	6,13
9	3	6,87	5,77
10	3	10,63	5,01
1	4	4,92	4,60
2	4	9,22	6,39
3	4	4,88	4,47
4	4	7,55	9,84
5	4	5,40	4,98
6	4	8,03	10,74
7	4	8,31	5,91
8	4	6,08	9,75
9	4	4,72	5,79
10	4	7,54	6,18
11	4	5,38	6,86
12	4	6,21	4,17
13	4	5,29	6,88
14	4	5,12	4,83
15	4	9,02	7,71
16	4	7,16	6,75
17	4	5,10	6,17
18	4	3,09	6,00
19	4	9,29	6,47
20	4	4,35	5,08
1	1	12,44	8,01
2	1	7,75	7,55
3	1	4,65	5,43
4	1	8,90	6,03
5	1	5,14	8,05
6	1	2,13	4,71
7	1	8,54	12,02
8	1	2,46	3,86
9	1	4,92	5,22
10	1	5,28	5,43
11	1	4,34	5,23
12	1	6,73	7,27
13	1	5,30	6,08
14	1	7,78	11,00
15	1	4,12	4,40
16	1	9,00	7,94
17	1	6,96	4,19
18	1	6,65	5,33
19	1	5,66	6,54
20	1	6,61	5,91
21	1	11,08	7,42
22	1	4,73	3,93
23	1	4,05	4,02

Equoral® capsules

Table 21 Elimination characteristic: $t_{1/2}$ (h)

S. No.	C. No.	Neoral /R/	Equoral /T/
24	1	5,77	5,44
25	1	6,62	5,54
26	1	6,29	6,83
27	1	2,83	3,72
28	1	5,57	7,71
29	1	2,86	3,10
30	1	7,67	6,92
31	1	10,77	6,77
32	1	6,98	9,65
33	1	7,84	4,27
34	1	8,61	7,53
35	1	13,96	11,33
36	1	8,25	10,17
37	1	8,32	6,87
38	1	6,53	7,01
39	1	6,21	5,43
40	1	5,38	7,37
n		70,00	70,00
Geom. Mean		6,26	6,31
Exp (mean $\pm$ SD,		4,37	4,65
Ln-data)		8,98	6,57
Median		6,41	6,15
Min.		2,13	3,10
Max.		13,96	12,12

paired t test

0,13 (NS)

Equoral® capsules

Table 22 Bioavailability characteristic: AUC_T (ng/ml.h)

S. No.	C. No.	Neoral /R/	Equoral /T/	T/R
1	3	3455	3557	1,03
2	3	4819	4277	0,93
3	3	4480	4297	0,96
4	3	4104	4307	1,05
5	3	3855	3830	1,05
6	3	5642	3630	0,64
7	3	4557	4200	0,92
8	3	4655	4488	0,96
9	3	4786	4571	0,96
10	3	3877	5046	1,30
1	4	2959	3068	1,04
2	4	3289	3524	1,07
3	4	3058	3230	1,06
4	4	8148	5449	0,67
5	4	3399	3457	1,02
6	4	4286	5359	1,25
7	4	6338	5777	0,91
8	4	4170	5315	1,27
9	4	4562	5961	1,31
10	4	4889	5005	1,02
11	4	1795	2636	1,47
12	4	4441	3417	0,77
13	4	2507	2122	0,85
14	4	2138	1715	0,80
15	4	3691	3707	1,00
16	4	1228	1891	1,38
17	4	2523	3360	1,33
18	4	1996	2465	1,23
19	4	3278	3399	1,04
20	4	2439	3313	1,36
1	1	3888	2905	0,75
2	1	3371	3727	1,11
3	1	1129	1014	0,90
4	1	1542	1377	0,89
5	1	1847	1685	1,03
6	1	520	521	1,00
7	1	2024	2537	1,25
8	1	768	935	1,22
9	1	2932	3529	1,20
10	1	2188	2805	1,20
11	1	985	1162	1,20
12	1	3980	3281	0,82
13	1	2010	2084	1,04
14	1	4211	3903	0,93
15	1	426	418	0,98
16	1	1805	1810	1,13
17	1	3041	2790	0,92
18	1	2827	2929	1,04
19	1	3474	3604	1,04
20	1	4212	4248	1,01
21	1	5484	5383	0,98
22	1	4862	4742	1,02
23	1	3511	3610	1,03

Equoral® capsules

Table 22 Bioavailability characteristic: AUC_t (ng/ml.h)

S. No.	C. No.	Neoral /R/	Equoral /T/	T/R
24	1	4198	4189	1,00
25	1	4819	4948	1,03
26	1	4243	3981	0,94
27	1	2984	3185	1,07
28	1	3171	3014	0,95
29	1	2487	2301	0,93
30	1	2429	2703	1,11
31	1	4800	4747	0,99
32	1	2526	2443	0,97
33	1	2889	3863	1,34
34	1	4270	5270	1,23
35	1	7405	7329	0,99
36	1	3338	3158	0,95
37	1	4189	3981	0,95
38	1	8510	8251	0,96
39	1	2909	2748	0,94
40	1	2284	1957	0,86
n		70	70	70
Geom. Mean		3038,71	3107,92	1,02
Exp (mean +/- SD, Ln-data)		1737,84	1821,05	
Median		5313,98	5304,18	
Min.		3385	3490,5	
Max.		426	418	
		8148	7329	
90%-confidence limits		0,99	1,056	
paired t-test	1,185	p = 0,25		

Equoral® capsules

Table 23 Bioavailability characteristic: C max (ng/ml)

S.No.	C.No.	Neoral /R/	Equoral /T/	T/R
1	3	693	791	1,14
2	3	1067	768	0,72
3	3	1068	1241	1,16
4	3	1157	1069	0,95
5	3	1019	998	0,98
6	3	1026	1179	1,15
7	3	1052	903	0,86
8	3	1104	1006	0,91
9	3	1091	912	0,84
10	3	1106	1091	0,99
1	4	582	884	1,57
2	4	908	824	0,91
3	4	782	916	1,17
4	4	1586	814	0,51
5	4	1116	1046	0,94
6	4	724	916	1,27
7	4	1238	716	0,58
8	4	1032	1008	0,98
9	4	1058	1354	1,28
10	4	1196	1260	1,05
11	4	468	744	1,60
12	4	912	304	0,33
13	4	540	306	0,57
14	4	452	238	0,53
15	4	666	674	0,97
16	4	188	252	1,34
17	4	533	995	1,87
18	4	437	688	1,57
19	4	541	465	0,86
20	4	399	636	1,59
1	1	998	832	0,83
2	1	958	960	1,00
3	1	283	263	0,93
4	1	557	457	0,82
5	1	808	560	0,92
6	1	239	210	0,88
7	1	803	761	0,95
8	1	300	356	1,19
9	1	667	1241	1,81
10	1	751	830	1,11
11	1	401	460	1,15
12	1	1050	693	0,66
13	1	696	634	0,91
14	1	1231	972	0,79
15	1	298	183	0,62
16	1	482	593	1,23
17	1	916	703	0,77
18	1	709	792	1,12
19	1	893	874	0,98
20	1	890	899	1,01
21	1	1073	1105	1,03
22	1	769	722	0,94
23	1	711	693	0,97

Table 23 Bioavailability characteristic: C max (ng/ml)

S.No.	C.No.	Neoral /R/	Equoral /T/	T/R
24	1	1000	968	0,97
25	1	990	1120	1,13
26	1	890	770	0,87
27	1	640	701	1,10
28	1	795	834	1,05
29	1	526	579	1,10
30	1	968	1109	1,15
31	1	794	1371	1,73
32	1	538	612	1,14
33	1	784	867	0,85
34	1	740	1196	1,62
35	1	1373	1327	0,97
36	1	640	661	1,03
37	1	679	661	0,97
38	1	1170	1003	0,86
39	1	498	482	0,97
40	1	376	344	0,91
n		70	70	70
Geom. Mean		724,92	717,35	0,99
Exp (mean +/- SD, Ln-data)		481,40	448,77	
Median		1138,96	1146,68	
Min.		763	780,5	
Max.		188	183	
		1586	1371	
90%-confidence limits		0,93	1,05	
paired t-test	0,294	p = 0,77		

Equoral® capsules

Table 24 Bioavailability characteristic: C min (ng/ml)

S.No.	C.No.	Neoral /R/	Equoral /T/	T/R
1	3	133	180	1,35
2	3	167	192	1,15
3	3	158	143	0,91
4	3	174	188	1,08
5	3	105	118	1,10
6	3	206	138	0,67
7	3	121	134	1,11
8	3	148	176	1,19
9	3	165	176	1,07
10	3	132	168	1,18
1	4	98	105	1,07
2	4	127	134	1,08
3	4	89	91	1,02
4	4	344	320	0,93
5	4	101	103	1,02
6	4	198	243	1,24
7	4	248	286	1,15
8	4	151	242	1,60
9	4	137	176	1,28
10	4	190	152	0,80
11	4	55	89	1,62
12	4	176	119	0,68
13	4	76	81	1,07
14	4	73	75	1,03
15	4	149	164	1,10
16	4	57	71	1,25
17	4	70	95	1,36
18	4	31	60	1,94
19	4	140	178	1,27
20	4	90	113	1,26
1	1	169	107	0,63
2	1	122	120	0,98
3	1	32	22	0,69
4	1	48	39	0,81
5	1	41	48	1,17
6	1	35	23	0,66
7	1	65	97	1,49
8	1	28	16	0,57
9	1	85	98	1,15
10	1	60	70	1,40
11	1	39	28	0,72
12	1	138	155	1,14
13	1	57	54	0,95
14	1	141	150	1,08
15	1	27	22	0,81
16	1	51	57	1,12
17	1	89	81	0,91
18	1	93	83	0,89
19	1	109	135	1,24
20	1	154	144	0,94
21	1	268	230	0,86
22	1	176	149	0,85
23	1	101	98	0,97

Table 24 Bioavailability characteristic: C min (ng/ml)

S.No.	C.No.	Neoral /R/	Equoral /T/	T/R
24	1	152	140	0,92
25	1	190	141	0,74
26	1	132	151	1,14
27	1	55	67	1,22
28	1	113	99	0,88
29	1	38	37	0,95
30	1	52	52	1,00
31	1	238	169	0,71
32	1	70	105	1,50
33	1	88	130	1,48
34	1	194	215	1,11
35	1	332	354	1,07
36	1	109	128	1,17
37	1	203	174	0,86
38	1	256	281	1,02
39	1	122	109	0,89
40	1	89	83	0,93
n		70	70	70
Geom. Mean		104,20	107,30	1,03
Exp (mean +/- SD,		58,21	58,03	
Ln-data)		193,19	205,48	
Median		117	119,5	
Min.		27	16	
Max.		344	354	
90%-confidence limits		0,98	1,08	
paired t-test	1,01	p = 0,31		

Equoral® capsules

Table 25 Bioavailability characteristic: PTF%

S. No.	C. No.	Neoral /R/	Equoral /T/	T/R
1	3	194,50	206,13	1,06
2	3	233,82	161,61	0,69
3	3	243,75	306,63	1,26
4	3	287,43	253,82	0,88
5	3	300,08	275,72	0,92
6	3	174,41	344,13	1,97
7	3	245,16	219,71	0,90
8	3	246,44	221,93	0,90
9	3	232,18	193,22	0,83
10	3	301,47	222,35	0,74
1	4	188,17	304,89	1,62
2	4	284,95	234,96	0,82
3	4	271,84	306,50	1,13
4	4	182,92	108,79	0,59
5	4	358,34	327,34	0,91
6	4	147,83	150,70	1,02
7	4	187,44	89,32	0,48
8	4	253,53	172,94	0,68
9	4	242,26	237,14	0,98
10	4	246,92	265,65	1,08
11	4	274,76	298,29	1,09
12	4	196,87	64,97	0,33
13	4	222,10	127,24	0,57
14	4	212,92	114,05	0,54
15	4	177,84	165,09	0,93
16	4	128,01	128,44	1,00
17	4	220,21	321,43	1,46
18	4	244,09	305,72	1,25
19	4	146,89	101,32	0,69
20	4	152,03	189,44	1,25
1	1	255,86	216,87	0,85
2	1	297,60	270,46	0,91
3	1	266,78	285,21	1,07
4	1	396,11	364,27	0,92
5	1	413,11	382,48	0,88
6	1	470,77	430,71	0,91
7	1	437,55	314,07	0,72
8	1	425,00	436,36	1,03
9	1	246,36	388,67	1,56
10	1	388,37	350,10	0,90
11	1	450,16	446,13	0,99
12	1	275,58	196,77	0,71
13	1	381,49	333,97	0,88
14	1	310,62	252,73	0,81
15	1	509,88	462,20	0,91
16	1	322,24	355,36	1,10
17	1	326,34	267,63	0,82
18	1	261,48	290,47	1,11
19	1	270,81	246,06	0,91
20	1	209,69	213,28	1,02
21	1	176,59	195,06	1,10
22	1	152,64	145,00	0,95
23	1	208,49	197,78	0,95

Equoral[®] capsules

Table 25 Bioavailability characteristic: PTF%

S. No.	C. No.	Neoral /R/	Equoral /T/	T/R
24	1	242,52	237,19	0,98
25	1	199,21	237,53	1,19
26	1	214,38	186,59	0,87
27	1	235,25	238,87	1,02
28	1	258,09	292,63	1,13
29	1	234,98	282,66	1,20
30	1	451,54	489,26	1,04
31	1	139,00	303,86	2,19
32	1	222,33	249,04	1,12
33	1	268,10	166,81	0,56
34	1	153,44	223,38	1,46
35	1	168,70	159,31	0,94
36	1	190,89	202,53	1,06
37	1	136,36	147,54	1,08
38	1	168,48	142,44	0,85
39	1	155,10	162,88	1,05
40	1	150,79	160,04	1,06
n		70,00	70,00	70
Geom. Mean		241,17	229,10	0,95
Exp (mean +/- SD,		172,53	152,31	
Ln-data)		337,13	344,59	
Median		243,13	237,36	
Min.		128,01	64,87	
Max.		509,85	469,26	
90%-confidence limits		0,90	1,01	

Equoral[®] capsules

Table 26 Bioavailability characteristic: MRT (h)

S. No.	C. No.	Neoral /R/	Equoral /T/	T/R
1	3	9,44	15,01	1,59
2	3	9,41	10,19	1,08
3	3	9,73	7,85	0,79
4	3	12,99	7,88	0,61
5	3	8,52	10,62	1,25
6	3	8,26	11,87	1,41
7	3	8,99	7,01	1,00
8	3	8,69	8,46	0,97
9	3	8,37	8,38	1,00
10	3	11,95	6,93	0,58
1	4	7,05	6,45	0,91
2	4	11,55	8,71	0,75
3	4	8,48	6,01	0,93
4	4	10,36	14,48	1,40
5	4	8,79	6,05	0,88
6	4	11,44	14,10	1,23
7	4	10,82	9,49	0,88
8	4	8,06	13,08	1,62
9	4	6,33	7,56	1,19
10	4	9,52	7,82	0,82
11	4	7,34	8,33	1,13
12	4	8,81	7,03	0,80
13	4	7,33	9,88	1,35
14	4	7,25	9,18	1,27
15	4	1,51	10,87	7,20
16	4	10,77	9,98	0,92
17	4	6,70	6,95	1,04
18	4	4,68	6,80	1,45
19	4	12,18	10,35	0,85
20	4	7,39	7,31	0,99
1	1	15,18	10,19	0,67
2	1	9,50	9,03	0,95
3	1	6,31	6,85	1,09
4	1	9,55	7,30	0,76
5	1	5,88	8,18	1,39
6	1	2,71	5,80	2,14
7	1	9,79	13,94	1,42
8	1	3,45	5,09	1,48
9	1	7,08	6,92	0,98
10	1	5,95	6,38	1,07
11	1	5,29	5,98	1,13
12	1	8,81	10,49	1,19
13	1	8,29	6,81	1,08
14	1	9,47	12,97	1,37
15	1	4,95	5,34	1,08
16	1	10,21	9,32	0,91
17	1	7,82	5,53	0,71
18	1	8,10	8,66	0,82
19	1	7,27	8,50	1,17
20	1	9,81	8,19	0,85
21	1	14,82	10,21	0,69
22	1	7,63	6,91	0,91
23	1	6,38	6,47	1,01

Equoral® capsules

Table 26 Bioavailability characteristic: MRT (h)

S. No.	C. No.	Neoral /R/	Equoral /T/	T/R
24	1	7,79	7,51	0,98
25	1	8,82	7,01	0,79
26	1	7,77	9,28	1,19
27	1	5,07	5,52	1,09
28	1	8,01	9,39	1,17
29	1	4,36	4,24	0,97
30	1	7,29	6,53	0,90
31	1	14,61	9,05	0,62
32	1	7,73	12,30	1,59
33	1	9,00	8,70	0,74
34	1	12,07	9,96	0,83
35	1	17,91	15,10	0,84
36	1	8,91	13,22	1,48
37	1	12,04	10,21	0,85
38	1	9,48	10,18	1,07
39	1	9,38	8,57	0,91
40	1	8,38	10,31	1,23
n		70,00	70,00	70
Geom. Mean		8,01	8,40	1,05
Exp (mean $\pm$ SD, Ln-data)		5,47	6,33	
Median		11,77	11,15	
Min.		8,32	8,36	
Max.		1,51	4,24	
		17,91	15,10	
90%-confidence limits		0,89	1,21	

Equoral® capsules

Table 27 Blood trough levels (ng/ml)

S. No.	C. No.	Neoral 7	Equoral 18	Neoral 35
1	3	168	168	174
2	3	177	210	196
3	3	169	160	182
4	3	248	201	234
5	3	123	132	163
6	3	147	138	142
7	3	152	141	144
8	3	178	270	157
9	3	144	168	156
10	3	203	203	166
1	4	150	96	135
2	4	202	157	162
3	4	115	79	141
4	4	161	434	408
5	4	554	111	150
6	4	266	284	194
7	4	296	210	287
8	4	210	214	256
9	4	203	261	225
10	4	152	211	182
11	4	120	54	64
12	4	122	175	108
13	4	132	80	142
14	4	58	79	118
15	4	77	166	163
16	4	86	50	124
17	4	142	114	86
18	4	81	68	49
19	4	108	234	176
20	4	180	151	120
1	1	157	148	98
2	1	168	179	174
3	1	43	32	31
4	1	59	46	49
5	1	40	37	34
6	1	21	26	12
7	1	93	90	90
8	1	23	23	37
9	1	89	98	131
10	1	65	69	87
11	1	31	27	36
12	1	166	187	170
13	1	53	46	65
14	1	146	147	178
15	1	10	15	15
16	1	43	88	44
17	1	85	167	99
18	1	91	100	83
19	1	124	133	130
20	1	147	139	118
21	1	261	201	221
22	1	133	151	133

Equoral® capsules

Table 27 Blood trough levels (ng/ml)

S. No.	C. No.	Neoral -7	Equoral 18	Neoral 35
23	1	119	108	119
24	1	151	162	151
25	1	189	196	205
26	1	123	136	107
27	1	77	89	79
28	1	93	91	62
29	1	41	53	42
30	1	70	83	70
31	1	289	263	263
32	1	142	119	149
33	1	183	153	198
34	1	189	177	156
35	1	317	361	334
36	1	114	123	121
37	1	178	156	156
38	1	239	246	251
39	1	101	109	98
40	1	71	61	77
n		70	70	70
Geom. Mean		116,20	117,23	116,12
Exp (mean +/- SD, Ln-data)		58,47	59,66	59,06
Median		137,6	138,5	138
Min.		10	15	12
Max.		554	434	406

Table 28 Bioavailability characteristic: T max (h)

S.No.	C.No.	Neoral /R/	Equoral /T/	Diff (T-R)
1	3	3	2	-1
2	3	2	1	-1
3	3	2	1,5	-0,5
4	3	1	1	0
5	3	1,5	1,5	0
6	3	2	0,5	-1,5
7	3	2	2	0
8	3	2	2	0
9	3	2	2	0
10	3	1,5	2	0,5
1	4	1,5	2	0,5
2	4	1,5	2	0,5
3	4	1,5	1,5	0
4	4	2	3	1
5	4	1	1	0
6	4	3	1,5	-1,5
7	4	1,5	2	0,5
8	4	2	3	1
9	4	1,5	2	0,5
10	4	1	1	0
11	4	1,5	1	-0,5
12	4	1,5	1,5	0
13	4	2	2	0
14	4	2	4	2
15	4	1,5	2	0,5
16	4	2	3	1
17	4	1,5	1	-0,5
18	4	3	2	-1
19	4	1,5	4	2,5
20	4	2	2	0
1	1	1	1,5	0,5
2	1	1,5	1	-0,5
3	1	2	1,5	-0,5
4	1	1,5	1,5	0
5	1	1,5	1	-0,5
6	1	1	1,5	0,5
7	1	1	1	0
8	1	1,5	1,5	0
9	1	1,5	2	0,5
10	1	2	1,5	-0,5
11	1	1,5	1,5	0
12	1	1,5	2	0,5
13	1	1,5	2	0,5
14	1	1,5	1,5	0
15	1	1	1,5	0,5
16	1	1,5	2	0,5
17	1	1,5	1,5	0
18	1	1,5	1,5	0
19	1	1,5	1,5	0
20	1	1	1,5	0,5
21	1	1,5	1,5	0
22	1	1,5	2	0,5
23	1	1,5	1,5	0

Equoral[®] capsules

Table 28 Bioavailability characteristic: T max (h)

S.No.	C.No.	Neoral /R/	Equoral /T/	Diff (T-R)
24	1	1,5	1,5	0
25	1	1,5	1,5	0
26	1	2	1,5	-0,5
27	1	1,5	1,5	0
28	1	2	2	0
29	1	2	1,5	-0,5
30	1	1	1,5	0,5
31	1	2	1	-1
32	1	1	1,5	0,5
33	1	1	2	1
34	1	4	1,5	-2,5
35	1	1,5	1	-0,5
36	1	2	2	0
37	1	1,5	1,5	0
38	1	2	1,5	-0,5
39	1	2	2	0
40	1	2	2	0
n		70	70	70
Median		1,5	1,5	0
Min		1	0,5	-2,5
Max		4	4	2,5

Equoral[®] capsules

Table 28 Sparse sampling (ng/ml)

S. No.	C. No.	Neoral			Equoral			Codif
		C0	C1	C2	C0	C1	C2	
1	3	118	896	722	111	737	867	7
2	3	175	585	492	219	248	772	-44
3	3	175	384	491	218	248	771	-43
4	3	220	833	715	237	238	418	-17
5	3	127	167	552	125	757	884	2
6	3	214	965	825	214	965	825	0
7	3	132	94	815	163	513	810	-21
8	3	168	896	785	178	882	925	-10
9	3	166	582	896	176	821	927	-10
10	3	248	1098	921	188	812	973	80
1	4	102	548	842	114	238	622	-12
2	4	247	948	682	123	140	952	124
3	4	108	454	914	101	314	580	7
4	4	447	742	1808	387	1578	1592	60
5	4	125	1012	738	93	912	678	32
6	4	272	478	720	303	373	884	-31
7	4	298	568	962	280	198	1146	38
8	4	257	528	1066	177	201	908	80
9	4	193	488	1048	211	420	960	-18
10	4	193	1802	1006	174	694	956	19
11	4	76	314	626	73	244	388	3
12	4	242	720	448	87	58	85	155
13	4	196	541	584	202	209	282	-6
14	4	225	250	320	79	90	271	146
15	4	208	728	600	173	598	840	35
16	4	107	402	422	91	161	395	18
17	4	167	797	605	114	304	608	53
18	4	65	337	403	63	169	277	2
19	4	227	587	568	216	743	794	11
20	4	181	169	407	138	280	503	43
1	1	138	978	635	172	517	1009	-34
2	1	142	987	893	158	1028	795	-16
3	1	43	185	194	28	49	166	15
4	1	64	727	361	44	283	520	20
5	1	48	690	390	34	483	410	14
6	1	20	178	163	13	250	136	7
7	1	82	779	423	95	938	513	-3
8	1	36	388	176	24	342	166	12
9	1	113	1147	819	87	1203	982	26
10	1	88	568	679	58	287	641	8
11	1	38	100	323	28	147	287	10
12	1	183	827	834	159	820	875	4
13	1	50	199	641	53	636	352	-3
14	1	181	658	656	129	1185	772	32
15	1	21	194	122	15	71	116	6
16	1	43	209	633	59	273	789	-16
17	1	97	687	590	82	394	703	15
18	1	87	610	583	99	600	562	-12
19	1	130	789	702	137	753	766	-7
20	1	133	751	745	143	787	805	-10
21	1	242	913	799	228	853	931	14
22	1	143	733	696	138	719	733	5

Equoral[®] capsules

-41	-145
337	-280
138	-280
595	297
-590	-312
0	0
-419	5
214	-140
-39	-31
484	-52
310	220
808	-270
140	334
-838	218
100	68
103	-184
370	-184
327	158
48	86
808	50
70	238
662	363
332	322
160	49
130	-240
241	27
493	-1
188	128
-178	-226
-111	-96
461	-374
-81	98
136	28
444	-159
207	-20
-72	27
-159	-90
28	10
-58	-163
279	38
-47	36
7	-141
-437	289
-527	-116
123	6
-64	-156
273	-113
10	21
18	-64
-16	-60
80	-132
14	-37

Equoral® capsules

23	1	107	698	502	118	672	560	-11
24	1	140	558	922	158	579	1013	-16
25	1	174	980	845	191	942	801	-17
26	1	117	733	572	125	758	582	-8
27	1	71	815	543	69	631	573	2
28	1	106	358	785	109	758	582	-3
29	1	48	485	526	84	508	512	-18
30	1	76	966	713	92	1124	742	-16
31	1	193	514	847	208	310	805	-15
32	1	96	408	854	106	1011	305	-10
33	1	120	483	820	151	854	743	-31
34	1	168	910	598	198	474	745	-30
35	1	368	883	865	323	1297	960	45
36	1	128	401	687	122	396	655	6
37	1	157	530	532	178	501	561	-21
38	1	249	612	983	239	653	952	10
39	1	110	272	482	101	238	497	9
40	1	57	143	304	83	162	287	-8
N		70	70	70	70	70	70	70
geo-mean		122,91	518,74	604,30	113,87	401,02	590,74	9,142857
SD +		232,84	952,59	956,45	228,19	953,52	1049,37	37,17654
SD -		64,88	282,48	381,81	57,13	168,66	332,56	
median		132,5	583,5	651,5	125	503,5	737,5	
min		20	94	122	13	49,00	85	
max		447	1802	1808	387	1578	1592	

Equoral[®] capsules

28	-58
-21	-91
38	-56
-23	-10
-18	-30
-400	213
-41	14
-158	-29
204	-158
-803	549
-371	77
436	-147
-414	-95
5	32
29	-28
-41	11
38	-15
-19	17
70	70
80,05714	-10,7
314,3617	170,6282

Equoral® capsules

14.2.3 Cyclosporine dose – descriptive statistics

Table 30 Cyclosporine doses

Day	Valid N	Mean	Confidence limits for mean		Median	Mode	Frequency of mode
			Lower boundary	Upper boundary			
Dose -7	70	188.07	167.90	204.24	150.00	150	19.00
Dose 0	70	185.38	167.05	203.67	150.00	150	19.00
Dose 14	70	184.29	165.82	202.75	150.00	150	19.00
Dose 18	70	184.29	165.82	202.75	150.00	150	19.00
Dose 21	70	184.29	165.82	202.75	150.00	150	19.00
Dose 28	70	184.29	165.82	202.75	150.00	150	19.00
Dose 35	70	181.79	163.72	199.85	150.00	150	20.00

Day	Minimum	Maximum	Lower quartile	Upper quartile	Quantile	Variance	Std Dev.
Dose -7	50.00	400.00	150.00	250.00	100.00	5808.6	76.21
Dose 0	50.00	400.00	125.00	250.00	125.00	5898.6	76.79
Dose 14	50.00	400.00	125.00	250.00	125.00	5999.5	77.46
Dose 18	50.00	400.00	125.00	250.00	125.00	5999.5	77.46
Dose 21	50.00	400.00	125.00	250.00	125.00	5999.5	77.46
Dose 28	50.00	400.00	125.00	250.00	125.00	5999.5	77.46
Dose 35	50.00	400.00	125.00	250.00	125.00	5741.3	75.77

Equoral[®] capsules

14.3 Safety Data

14.3.1 Display of adverse events

Table 31
Study Period I. - Neoral N=70

	Mild		Moderate		Severe		Total		Total
	Related	NR*	Related	NR*	Related	NR*	Related	NR*	R+NR
<i>Diseases of GIT</i>									
Gingival hypertrophy (K06.1)					1(1.4%) 14/1**		1(1.4%)		1(1.4%)
<i>Symptoms, signs and ill-defined conditions</i>									
Fever (R50.9)				1(1.4%) 07/4**				1(1.4%)	1(1.4%)
							1(1.4%)	1(1.4%)	2(2.8%)

* NR = not related

** patient's identification number

Table 32
Study Period II. - Equoral N=70

	Mild		Moderate		Severe		Total		Total
	Related	NR*	Related	NR*	Related	NR*	Related	NR*	R+NR
<i>Infectious or parasitic diseases</i>									
Oral thrush (B37.9)	1(1.4%) 20/1**		14 (20%) 01/1** 03/1** 05/1** 06/1** 07/1** 08/1** 09/1** 11/1** 12/1** 13/1** 14/1** 15/1** 16/1** 17/1**				15(21.4%)		15 (21.4%)
White tongue (B37.9)	1(1.4%) 18/1**						1(1.4%)		1(1.4%)
<i>Diseases of GIT</i>									
Gingival hypertrophy (K06.1)					1(1.4%) 14/1**		1(1.4%)		1(1.4%)
<i>Diseases of the nervous system</i>									
Headache (G44.8)						1 (1.4%) 09/1**		1(1.4%)	1(1.4%)

Equoral® capsules

Symptoms, signs and ill-defined conditions									
Epistaxis (R04.0)		1 (1.4%) 09/1**						1(1.4%)	1(1.4%)
Others									
Red right eye			1(1.4%) 08/1**				1(1.4%)		1(1.4%)
Itching	1(1.4%) 06/1**						1(1.4%)		1(1.4%)
							19(27.1%)	2(2.9%)	21(30%)

* NR = not related

** patient's identification number

Table 33

Study Period III. - Neurai N=70

	Mild		Moderate		Severe		Total		Total
	Related	NR*	Related	NR*	Related	NR*	Related	NR*	R+NR
Infectious or parasitic diseases									
Oral thrush (B37.0)	1(1.4%) 20/1**		14(20%) 01/1** 03/1** 05/1** 06/1** 08/1** 08/1** 10/1** 11/1** 12/1** 13/1** 14/1** 15/1** 16/1** 17/1**				15 (21.4%)		15 (21.4%)
Diseases of GIT									
Gingival hypertrophy					1(1.4%) 14/1**		1(1.4%)		1(1.4%)
Others									
Red right eye			1(1.4%) 06/1**				1(1.4%)		1(1.4%)
Itching	1(1.4%) 06/1**						1(1.4%)		1(1.4%)
							18 (25.7%)		18 (25.7%)

* NR = not related

** patient's identification number

Equoral® capsules

Table 34
Naoral (period I and II) N=70

	Mild		Moderate		Severe		Total		Total
	Related	NR*	Related	NR*	Related	NR*	Related	NR*	R+NR
Infectious or parasitic diseases									
Oral thrush (B37.9)	1(1.4%) 20/1**		14(20%) 01/1** 03/1** 05/1** 06/1** 08/1** 09/1** 10/1** 11/1** 12/1** 13/1** 14/1** 15/1** 16/1** 17/1**				15 (21.4%)		15 (21.4%)
Diseases of GIT									
Gingival hypertrophy					1(1.4%) 14/1**		1(1.4%)		1(1.4%)
Symptoms, signs and ill-defined conditions									
Fever (R50.9)				1(1.4%) 07/4**				1(1.4%)	1(1.4%)
Others									
Red right eye			1(1.4%) 06/1**				1(1.4%)		1(1.4%)
Itching	1(1.4%) 08/1**						1(1.4%)		1(1.4%)
							18 (25.7%)	1(1.4%)	19 (27.1%)

* NR = not related

** patient identification number

Equoral[®] capsules

14.3.2 Listing of death, other serious and certain other significant adverse events

Not applicable

Equoral[®] capsules

14.3.3 Narratives of death, other serious and certain other significant adverse events

Not applicable

Equoral[®] capsules

14.3.4 Abnormal laboratory value listings (each patient)

See Section 16.2.8

Equoral[®] capsules

14.3.5 Summary statistics for laboratory values

14.3.5.1 Haematology

Table 35 Haematology – descriptive statistics (day -7)

	Valid N	Mean	Confidence interval for mean		Median	Mode	Frequency
			Lower bound	Upper bound			
Haematocrit (%)	70.00	39.81	38.57	41.05	39.45	41.0	4.00
Haemoglobin (g/dL)	70.00	13.01	12.57	13.46	13.00	13.0	7.00
RBC ($10^{12}/L$)	70.00	4.43	4.18	4.67	4.22	3.8	4.00
WBC ($10^9/L$)	70.00	7.17	6.68	7.67	6.62	6.4	3.00
Neutrophils (%)	70.00	63.40	61.32	65.48	63.25	59.0	3.00
Basophils (%)	70.00	0.48	0.43	0.54	0.46	0.40	13.00
Eosinophils (%)	70.00	1.47	1.16	1.78	1.30	1.0	7.00
Lymphocytes (%)	70.00	24.28	22.39	26.18	24.80	Multiple	
Monocytes (%)	70.00	6.08	5.45	6.72	5.50	3.0	5.00
Platelets ($10^9/L$)	69.00	239.29	226.45	252.13	230.00	215.0	4.00

	Minimum	Maximum	Lower quartile	Upper quartile	Range	Variance	Std. Dev.
Haematocrit (%)	27.00	53.00	37.00	43.00	26.00	27.13	5.21
Haemoglobin (g/dL)	7.80	18.30	12.00	14.00	10.50	3.50	1.87
RBC ($10^{12}/L$)	1.70	7.77	3.80	5.09	6.07	1.03	1.01
WBC ($10^9/L$)	3.63	14.90	5.73	8.60	11.27	4.34	2.08
Neutrophils (%)	40.00	80.80	57.60	69.00	40.80	76.30	8.73
Basophils (%)	0.10	1.00	0.30	0.60	0.90	0.05	0.23
Eosinophils (%)	0.10	9.70	0.77	1.70	9.60	1.70	1.30
Lymphocytes (%)	9.00	41.80	18.00	29.00	32.80	63.10	7.94
Monocytes (%)	2.00	13.46	4.30	7.80	11.46	7.18	2.68
Platelets ($10^9/L$)	127.00	421.00	203.00	272.00	294.00	2854.74	53.43

	Abnormal values	Decreased	Increased
Haematocrit (%)	38	34	4
Haemoglobin (g/dL)	44	40	4
RBC ($10^{12}/L$)	44	33	11
WBC ($10^9/L$)	4	2	2
Neutrophils (%)	6	0	6
Basophils (%)	0	0	0
Eosinophils (%)	26	22	4
Lymphocytes (%)	24	23	1
Monocytes (%)	4	0	4
Platelets ($10^9/L$)	3	2	1

Equoral® capsules

Table 36 Haematology—descriptive statistics (day 21)

	Valid N	Mean	Confidence interval for mean		Median	Mode	Frequency
			Lower bound	Upper bound			
Haematocrit (%)	69	39.4008	38.0890	40.7052	39.0000	Multiple	6
Haemoglobin (g/dL)	69	12.9118	12.4518	13.3714	12.9000	13.10000	3
RBC ($10^{12}/L$)	69	4.4297	4.2129	4.6466	4.1400	4.100000	5
WBC ($10^9/L$)	70	6.8429	6.4175	7.2682	6.4900	6.300000	3
Neutrophils (%)	69	63.6572	61.8100	65.9045	64.0000	66.000000	14
Basophils (%)	69	0.5116	0.4472	0.5760	0.5000	0.5000000	6
Eosinophils (%)	69	1.5307	1.1943	1.8671	1.4000	1.000000	6
Lymphocytes (%)	70	25.0178	23.0317	27.0034	23.9000	Multiple	6
Monocytes (%)	69	6.2036	5.3821	7.0152	5.6000	2.000000	6
Platelets ($10^9/L$)	69	227.8406	216.9035	239.7777	228.0000	Multiple	

	Minimum	Maximum	Lower quartile	Upper quartile	Range	Variance	Std. Dev.
Haematocrit (%)	26.8000	51.8000	36.0000	42.0000	24.9000	29.483	5.43072
Haemoglobin (g/dL)	8.9000	17.8000	12.0000	13.8000	8.9000	3.663	1.91392
RBC ($10^{12}/L$)	2.5400	6.5000	3.8400	6.0400	3.9600	0.816	0.90270
WBC ($10^9/L$)	3.7400	14.0000	5.8900	7.6000	10.2600	3.162	1.78375
Neutrophils (%)	42.7000	79.0000	68.8000	70.3000	36.3000	72.629	8.52224
Basophils (%)	0.0000	1.4000	0.3000	0.8000	1.4000	0.072	0.26822
Eosinophils (%)	0.1000	10.8000	0.7800	2.0000	10.7000	1.961	1.40036
Lymphocytes (%)	8.2000	48.2000	18.9000	31.8000	40.0000	69.363	8.32847
Monocytes (%)	2.0000	21.1000	4.7000	7.2000	19.1000	11.413	3.37833
Platelets ($10^9/L$)	110.0000	355.0000	203.0000	258.0000	245.0000	2469.195	49.69099

	Abnormal values	Decreased	Increased
Haematocrit (%)	40	35	5
Haemoglobin (g/dL)	47	43	4
RBC ($10^{12}/L$)	47	37	10
WBC ($10^9/L$)	5	4	1
Neutrophils (%)	7	1	6
Basophils (%)	4	0	4
Eosinophils (%)	26	23	3
Lymphocytes (%)	25	22	3
Monocytes (%)	6	1	5
Platelets ($10^9/L$)	6	6	0

Equoral[®] capsules

COMPARISON OF ABNORMAL VALUES BETWEEN DAY -7 AND DAY 21

Haematocrit - abnormal values lower than lower limit of reference range

Day 21
 Day 7 - +
 - 31 5
 + 4 30

McNemar's chi-squared = 0.1111, df = 1, p-value = 0.7388
 No statistically significant difference was found out.

Haematocrit - abnormal values higher than upper limit of reference range

Day 21
 Day 7 - +
 - 64 2
 + 1 3

McNemar's chi-squared = 0.3333, df = 1, p-value = 0.5637
 No statistically significant difference was found out.

Haemoglobin - abnormal values lower than lower limit of reference range

Day 21
 Day 7 - +
 - 25 5
 + 2 38

McNemar's chi-squared = 1.2857, df = 1, p-value = 0.2568
 No statistically significant difference was found out.

Haemoglobin - abnormal values higher than upper limit of reference range

Day 21
 Day 7 - +
 - 64 2
 + 2 2

McNemar's chi-squared = 0, df = 1, p-value = 1
 No statistically significant difference was found out.

RBC - abnormal values lower than lower limit of reference range

Day 21
 Day 7 - +
 - 32 5
 + 1 32

McNemar's chi-squared = 2.8667, df = 1, p-value = 0.1025
 No statistically significant difference was found out.

RBC - abnormal values higher than upper limit of reference range

Day 21
 Day 7 - +
 - 57 2
 + 3 8

McNemar's chi-squared = 0.2, df = 1, p-value = 0.6547
 No statistically significant difference was found out.

Equoral[®] capsules

WBC - abnormal values lower than lower limit of reference range

Day 21

Day 7 - +

- 66 2

+ 0 2

McNemar's chi-squared = 2, df = 1, p-value = 0.1573
No statistically significant difference was found out.

WBC - abnormal values higher than upper limit of reference range

Day 21

Day 7 - +

- 66 0

+ 1 1

McNemar's chi-squared = 1, df = 1, p-value = 0.3173
No statistically significant difference was found out.

Neutrophils - abnormal values lower than lower limit of reference range

Day 21

Day 7 - +

- 69 1

+ 0 0

McNemar's chi-squared = 1, df = 1, p-value = 0.3173
No statistically significant difference was found out.

Neutrophils - abnormal values higher than upper limit of reference range

Day 21

Day 7 - +

- 63 1

+ 1 6

McNemar's chi-squared = 0, df = 1, p-value = 1
No statistically significant difference was found out.

Basophils - abnormal values lower than lower limit of reference range

Day 21

Day 7 - +

- 70 0

+ 0 0

McNemar's chi-squared = NaN, df = 1, p-value = NA
No statistically significant difference was found out.

Basophils - abnormal values higher than upper limit of reference range

Day 21

Day 7 - +

- 66 4

+ 0 0

McNemar's chi-squared = 4, df = 1, p-value = 0.0455
The difference was statistically significant.

Eosinophils - abnormal values lower than lower limit of reference range

Day 21

Day 7 - +

- 41 7

+ 6 16

McNemar's chi-squared = 0.0769, df = 1, p-value = 0.7815
No statistically significant difference was found out.

Equoral[®] capsules

Neutrophils - abnormal values higher than upper limit of reference range

Day 21
Day 7 - +
- 66 0
+ 1 3

McNemar's chi-squared = 1, df = 1, p-value = 0.3173
No statistically significant difference was found out.

Lymphocytes - abnormal values lower than lower limit of reference range

Day 21
Day 7 - +
- 48 1
+ 2 21

McNemar's chi-squared = 0.3333, df = 1, p-value = 0.5637
No statistically significant difference was found out.

Lymphocytes - abnormal values higher than upper limit of reference range

Day 21
Day 7 - +
- 67 2
+ 0 1

McNemar's chi-squared = 2, df = 1, p-value = 0.1573
No statistically significant difference was found out.

Monocytes - abnormal values lower than lower limit of reference range

Day 21
Day 7 - +
- 69 1
+ 0 0

McNemar's chi-squared = 1, df = 1, p-value = 0.3173
No statistically significant difference was found out.

Monocytes - abnormal values higher than upper limit of reference range

Day 21
Day 7 - +
- 63 3
+ 2 2

McNemar's chi-squared = 0.2, df = 1, p-value = 0.6547
No statistically significant difference was found out.

Platelets - abnormal values lower than lower limit of reference range

Day 21
Day 7 - +
- 63 5
+ 1 1

McNemar's chi-squared = 2.6867, df = 1, p-value = 0.1025
No statistically significant difference was found out.

Platelets - abnormal values higher than upper limit of reference range

Day 21
Day 7 - +
- 68 0
+ 1 0

McNemar's chi-squared = 1, df = 1, p-value = 0.3173
No statistically significant difference was found out.

Equoral[®] capsules

COMPARISON OF MEAN VALUES BETWEEN DAY -7 AND DAY 21

Test of numerical equality of mean values - Student's pair t-test ($\alpha = 0.05$)

$$H_0: \mu_{-7} = \mu_{21}$$

against

$$H_A: \mu_{-7} \neq \mu_{21}$$

	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
Haematocrit -7	39.81	5.21						
Haematocrit 21	39.4008	5.43072	69	0.4516942	2.495071	1.5036	68	0.1374
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
Haemoglobin -7	13.01	1.87						
Haemoglobin 21	12.9116	1.91392	69	0.1144928	0.690114	1.3761	68	0.177
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
Erythrocytes -7	4.43	1.01						
Erythrocytes 21	4.4297	0.90270	69	-0.03535232	0.636416	-0.4601	68	0.641
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
WBC -7	7.17	2.08						
WBC 21	6.6429	1.78375	70	0.5294286	7.284313	1.86	69	0.067
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
Neutrophils -7	63.40	8.73						
Neutrophils 21	63.8672	8.52224	69	0.1161159	15.12403	-0.1773	68	0.85
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
Basophils -7	0.48	0.23						
Basophils 21	0.5116	0.26833	68	-0.02275362	0.214485	-0.6629	68	0.51
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
Eosinophils -7	1.47	1.30						
Eosinophils 21	1.5307	1.40036	69	0.04942029	0.806406	0.7648	68	0.44

Equoral® capsules

	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
7								
Lymphocytes -7	24.28	7.94						
Lymphocytes 21	25.0178	8.32847	70	-0.7365714	8.484189	-1.3877	69	0.169
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
8								
Monocytes -7	6.08	2.68						
Monocytes 21	6.2036	3.37833	69	0.07463768	7.918003	-0.2482	68	0.804
	Mean	Standard deviation	N	Difference	Standard deviation of difference	t	df	p
13								
Platelets -7	239.28	53.43						
Platelets 21	227.8406	49.69099	68	11.96785	29.46534	3.3213	67	0.00145

Statistically significant difference was shown in platelets.

14.3.5.2 Blood chemistry

Table 37 Blood chemistry – descriptive statistics (day -7)

	Valid N	Mean	Confidence interval for mean		Median	Mode	Frequency
			Lower bound	Upper bound			
Creatinine	70	1.2386	1.1725	1.3068	1.2050	Multiple	
Urea	70	30.8571	28.5254	35.1888	28.0000	38.00000	5
Uric acid	68	8.5309	8.1979	8.8638	8.3500	Multiple	
ALAT	70	27.8286	19.2570	36.0001	20.5000	23.00000	6
ASAT	70	28.1571	21.3721	34.9422	19.0000	19.00000	10
GMT	70	30.9714	24.8841	37.0788	23.5000	15.00000	8
ALP	70	157.7571	137.2489	178.2653	144.0000	238.0000	4
Total bilirubin	70	0.8457	0.7535	0.9380	0.9000	.8000000	18
Amylase	67	94.5970	84.5483	104.8477	86.0000	66.00000	5
Protein	70	7.1790	7.0447	7.3133	7.0000	8.800000	9
Glucose	70	95.6857	91.5120	99.8594	92.5000	90.00000	5
Sodium	70	141.5286	140.1527	142.9044	141.0000	142.0000	14
Potassium	70	4.2228	4.1135	4.3322	4.1000	4.100000	9
Magnesium	70	2.0948	2.0196	2.1701	2.0000	2.000000	12
Chloride	70	106.6857	105.8298	107.5416	106.0000	104.0000	12
Calcium	70	9.8171	9.8412	9.9931	9.8000	9.800000	7
Phosphorus	70	3.5137	3.2891	3.7383	3.4000	3.700000	8
Triglycerides	70	158.8286	140.4204	178.8387	143.0000	Multiple	
Total cholesterol	70	192.9000	183.8036	201.9965	190.0000	Multiple	

	Minimum	Maximum	Lower	Upper	Range	Variance	Std.Dev.
Creatinine	0.8000	2.0200	1.0400	1.4500	1.4200	0.079	0.28117
Urea	10.0000	96.0000	18.0000	38.0000	86.0000	330.037	18.16883
Uric acid	1.7000	9.5000	5.5500	7.5000	7.8000	1.893	1.37572
ALAT	8.0000	241.0000	14.0000	28.0000	233.0000	1232.872	35.10942
ASAT	7.0000	213.0000	17.0000	27.0000	209.0000	809.728	28.45573
GMT	10.0000	178.0000	15.0000	40.0000	168.0000	666.057	25.81361
ALP	42.0000	445.0000	96.0000	222.0000	403.0000	7387.807	86.00834
Total bilirubin	0.3100	2.4800	0.6100	0.9000	2.1500	0.150	0.38889
Amylase	10.0000	211.0000	64.0000	126.0000	201.0000	1697.850	41.20498
Protein	6.1000	9.0000	6.8000	7.6000	2.9000	0.317	0.56324
Glucose	65.0000	165.0000	85.0000	104.0000	100.0000	308.393	17.50407
Sodium	130.0000	170.0000	138.0000	142.0000	40.0000	33.288	5.77029
Potassium	3.3000	5.2000	3.8000	4.5000	1.9000	0.210	0.45847
Magnesium	1.7000	3.6000	1.9000	2.2000	1.9000	0.100	0.31563
Chloride	99.0000	117.0000	104.0000	109.0000	16.0000	12.885	3.58961
Calcium	8.2000	12.2000	9.4000	10.2000	4.0000	0.544	0.73778
Phosphorus	2.0000	5.8000	2.8000	4.2000	3.8000	0.887	0.94191
Triglycerides	37.0000	517.0000	110.0000	189.0000	480.0000	8489.454	80.55716
Total cholesterol	117.0000	286.0000	163.0000	228.0000	171.0000	1465.398	38.14986

	Abnormal values	Decreased	Increased
Creatinine	35	1	34
Urea	8	0	8
Uric acid	35	3	32
ALAT	8	0	8
ASAT	10	0	10
GMT	9	1	8
ALP	12	2	10
Total bilirubin	7	0	7
Amylase	30	3	27
Protein	8	4	2
Glucose	9	3	6
Sodium	8	3	3
Potassium	10	5	5
Magnesium	7	0	7
Chloride	35	0	35
Calcium	11	2	9
Phosphorus	28	18	9
Triglycerides	29	3	26
Total cholesterol	28	1	27

Table 38 Blood chemistry - descriptive statistics (day 21)

	Valid N	Mean	Confidence interval for mean		Median	Mode	Frequency
			Lower bound	Upper bound			
Creatinine	70	1.2733	1.2023	1.3442	1.2850	Multiple	
Urea	70	31.4714	26.7148	36.2281	27.0000	20.00000	5
Uric acid	70	6.5829	6.1954	6.9304	6.6600	6.200000	5
ALAT	70	28.9143	18.8587	38.9699	18.0000	Multiple	
ASAT	70	24.8614	20.4496	29.3133	20.0000	Multiple	
GMT	70	31.5000	24.8888	38.1112	21.5000	14.00000	8
ALP	70	158.8867	135.3252	178.4483	140.0000	Multiple	
Total bilirubin	70	0.8703	0.7831	0.9754	0.8000	Multiple	
Amylase	68	82.2059	83.0721	101.3397	86.6000	Multiple	
Protein	70	7.1700	7.0368	7.3032	7.1000	6.700000	7
Glucose	70	96.0257	80.8743	101.9771	92.6000	95.00000	5
Sodium	70	141.1143	139.7218	142.5067	141.0000	144.0000	8
Potassium	70	4.2143	4.1078	4.3208	4.2000	4.200000	11
Magnesium	70	2.0686	1.9948	2.1426	2.0000	2.000000	12
Chloride	70	106.2143	105.3021	107.1284	105.0000	106.0000	16
Calcium	70	9.6900	9.6500	9.8300	9.6800	9.500000	9
Phosphorus	70	3.5427	3.3184	3.7661	3.5000	3.800000	5
Triglycerides	70	158.1429	141.5118	174.7739	147.5000	170.0000	3
Total cholesterol	70	181.3857	182.6287	200.1427	191.0000	200.0000	5

Equoral® capsules

	Minimum	Maximum	Lower	Upper	Range	Variance	Std.Dev.
Creatinine	0.5000	1.9200	1.0700	1.5000	1.3200	0.089	0.29752
Urea	9.0000	96.0000	18.0000	35.0000	67.0000	397.963	19.94901
Uric acid	1.5000	10.2000	5.3000	7.8000	8.7000	2.375	1.54124
ALAT	9.0000	309.0000	15.0000	28.0000	300.0000	1778.486	42.17209
ASAT	10.0000	127.0000	16.0000	24.0000	117.0000	345.474	18.58993
GMT	9.0000	162.0000	14.0000	42.0000	153.0000	768.775	27.72690
ALP	24.0000	472.0000	65.0000	220.0000	448.0000	8176.277	90.42277
Total bilirubin	0.2300	2.6000	0.6800	1.0400	2.3700	0.163	0.40318
Amylase	10.0000	175.0000	65.0000	114.5000	165.0000	1423.927	37.73496
Protein	6.0000	8.9000	6.8000	7.5000	2.9000	0.312	0.55882
Glucose	89.0000	265.0000	88.0000	89.0000	196.0000	622.985	24.95958
Sodium	130.0000	166.0000	138.0000	144.0000	36.0000	34.103	5.93975
Potassium	3.1000	6.2000	4.0000	4.4000	2.1000	0.200	0.44666
Magnesium	1.7000	4.0000	1.9000	2.1900	2.3000	0.096	0.31026
Chloride	100.0000	119.0000	104.0000	108.0000	19.0000	14.635	3.82562
Calcium	8.0000	11.3000	9.4000	10.1000	3.3000	0.345	0.58734
Phosphorus	1.6000	5.9000	3.0000	4.1000	4.1000	0.877	0.93885
Triglycerides	44.0000	409.0000	115.0000	180.0000	366.0000	4864.907	69.74888
Total cholesterol	125.0000	299.0000	163.0000	208.0000	174.0000	1348.791	36.72569

	Abnormal values	Decreased	Increased
Creatinine	37	2	35
Urea	10	1	9
Uric acid	33	1	32
ALAT	10	0	10
ASAT	7	0	7
GMT	11	1	10
ALP	12	4	8
Total bilirubin	12	1	11
Amylase	28	2	27
Protein	11	7	4
Glucose	5	1	4
Sodium	13	9	4
Potassium	11	6	5
Magnesium	2	0	2
Chloride	33	0	33
Calcium	7	3	4
Phosphorus	28	20	8
Triglycerides	30	1	29
Total cholesterol	26	0	26

Equoral® capsules

COMPARISON OF ABNORMAL VALUES BETWEEN DAY -7 AND DAY 21

ALAT – abnormal values higher than upper limit of normal

Day 21	
Day -7	- +
	- 60 2
	+ 0 8

McNemar's chi-squared = 2, df = 1, p-value = 0.1573
 No statistically significant difference was found out.

ASAT – abnormal values higher than upper limit of normal

Day 21	
Day -7	- +
	- 68 0
	+ 0 1

McNemar's chi-squared = 1.8, df = 1, p-value = 0.1797
 No statistically significant difference was found out.

GMT – abnormal values lower than lower limit of normal

Day 21	
Day -7	- +
	- 69 0
	+ 0 1

McNemar's chi-squared = NaN, df = 1, p-value = NA
 No statistically significant difference was found out.

GMT – abnormal values higher than upper limit of normal

Day 21	
Day -7	- +
	- 58 4
	+ 2 8

McNemar's chi-squared = 0.6667, df = 1, p-value = 0.4142
 No statistically significant difference was found out.

ALP – abnormal values lower than lower limit of normal

Day 21	
Day -7	- +
	- 66 2
	+ 0 2

McNemar's chi-squared = 1, df = 1, p-value = 0.3173
 No statistically significant difference was found out.

ALP – abnormal values higher than upper limit of normal

Day 21	
Day -7	- +
	- 66 2
	+ 0 2

McNemar's chi-squared = 2, df = 1, p-value = 0.1573
 No statistically significant difference was found out.

Equoral[®] capsules

COMPARISON OF MEAN VALUES BETWEEN DAY -7 AND DAY 21

Test of numerical equality of mean values – Student's pair t-test ($\alpha = 0.05$)

Hypotheses:

 H_0 : mean values are equal

against

 H_A : mean values are different (i.e. two-sided hypothesis)

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Creatinine -7	1.238571	0.281170						
Creatinine 21	1.273286	0.287520	70	-0.033714	0.189134	-1.86775	69	0.069897

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Urea -7	30.85929	18.41585						
Urea 21	31.21429	20.21328	70	-0.555000	5.779726	-0.803405	69	0.424498

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Uric acid -7	8.530882	1.375723						
Uric acid 21	8.518178	1.526248	68	0.014708	0.729806	0.199185	67	0.858528

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
ALAT -7	27.6286	35.10942						
ALAT 21	28.6143	42.17209	70	-1.285714	20.86289	-0.6735	69	0.5029

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
ASAT -7	28.1671	28.45573						
ASAT 21	24.6814	18.58893	70	3.276714	15.03184	1.9202	69	0.0728

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
GMT -7	30.9714	25.81361						
GMT 21	31.50000	27.72690	70	-0.5285714	12.58499	-0.3957	69	0.6936

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
ALP -7	157.7571	88.00934						
ALP 21	156.8857	90.42277	70	0.8714286	22.89388	0.3213	69	0.749

Equoral® capsules

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Total bilirubin -7	0.845714	0.388892						
Total bilirubin 21	0.985000	0.814281	70	-0.119286	0.752702	-1.32591	69	0.189242

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Amylase -7	94.48482	42.78144						
Amylase 21	91.19231	39.93858	65	3.292308	22.29611	1.190498	64	0.238248

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Protein -7	7.179000	0.563244						
Protein 21	7.170000	0.658818	70	0.009000	0.353349	0.213102	69	0.831676

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Glucose -7	85.68571	17.50407						
Glucose 21	83.86286	28.99456	70	1.722857	22.78849	0.632532	69	0.529130

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Sodium -7	139.4920	17.70360						
Sodium 21	139.1767	17.68378	70	0.315266	24.01898	0.108824	69	0.912887

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Potassium -7	4.222857	0.458470						
Potassium 21	4.214286	0.445658	70	0.008571	0.451645	0.168783	69	0.874303

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Magnesium -7	2.094857	0.315630						
Magnesium 21	2.088571	0.310281	70	0.026286	0.244607	0.899085	69	0.371734

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Chloride -7	108.6857	3.688610						
Chloride 21	108.2143	3.825516	70	0.471429	2.387901	1.651766	69	0.103128

Equoral® capsules

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Calcium -7	9.817143	0.737754						
Calcium 21	9.690000	0.587342	70	0.127143	0.550775	1.695830	69	0.062023

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Phosphorus -7	3.513714	0.941912						
Phosphorus 21	3.542714	0.936551	70	-0.029000	0.512075	-0.473820	69	0.637124

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Triglycerides -7	159.6286	80.55715						
Triglycerides 21	156.7286	71.71520	70	2.900000	40.62737	0.594286	69	0.554264

	Mean	Standard deviation	N	Difference	Standard Deviation of difference	t	df	p
Total cholesterol -7	192.9000	38.14965						
Total cholesterol 21	191.3857	35.72589	70	1.514266	21.20551	0.597459	69	0.552157

No test was statistically significant on $\alpha = 0.05$. It means that H_0 hypothesis could not be rejected and there is no difference between day -7 and day 21 in any parameter.

Equoral[®] capsules

14.3.6 Summary statistics for vital signs

Table 39 Vital signs – descriptive statistics

	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	757.00	79.16	78.52	79.79	80.00	80.00	102.00
Systolic pressure (mmHg)	758.00	124.23	123.27	125.19	125.00	120.00	158.00
Diastolic pressure (mmHg)	758.00	80.54	79.66	81.39	80.00	80.00	198.00
Body temperature (°C)	758.00	36.96	36.13	37.83	36.60	36.50	114.00
Body weight (kg)	758.00	65.35	64.45	66.25	64.00	58.00	24.00

Table 40 Vital signs – descriptive statistics

	Minimum	Maximum	Lower	Upper	Range	Quantile	Variance	Standard deviation
Radial pulse rate (bpm)	55.00	110.00	72.00	85.00	64.00	13.00	78.58	8.86
Systolic pressure (mmHg)	88.00	180.00	120.00	190.00	92.00	10.00	181.34	13.47
Diastolic pressure (mmHg)	20.00	110.00	72.00	90.00	90.00	18.00	143.66	11.99
Body temperature (°C)	28.60	38.40	36.40	36.78	337.40	0.38	141.74	11.91
Body weight (kg)	40.30	124.50	58.00	72.00	84.20	16.00	159.62	12.63

Table 41 Vital signs – descriptive statistics (day -7)

Day -7	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	69.00	80.33	79.07	82.60	80.00	2.00	8.00
Systolic pressure (mmHg)	70.00	126.87	123.50	130.24	130.00	30.00	17.00
Diastolic pressure (mmHg)	70.00	81.69	79.45	84.32	80.00	80.00	21.00
Body temperature (°C)	70.00	36.52	36.45	36.59	36.50	36.67	13.00
Body weight (kg)	70.00	65.73	62.64	68.82	65.90	Multiple	

Equoral® capsules

Table 42 Vital signs – descriptive statistics (day -7)

Day -7	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	60.00	100.00	72.00	88.00	40.00	16.00	86.73	9.42
Systolic pressure (mmHg)	82.00	180.00	120.00	135.00	88.00	15.00	189.88	14.14
Diastolic pressure (mmHg)	60.00	110.00	75.00	90.00	50.00	15.00	104.13	10.20
Body temperature (°C)	35.78	37.40	36.40	36.87	1.62	0.27	0.09	0.29
Body weight (kg)	41.00	123.00	55.00	74.70	82.00	19.70	168.03	12.96

Table 43 Vital signs – descriptive statistics (day 0)

Day 0	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	70.00	79.41	77.21	81.61	80.00	82.00	11.00
Systolic pressure (mmHg)	70.00	125.70	122.40	129.00	123.00	120.00	18.00
Diastolic pressure (mmHg)	70.00	82.29	79.83	84.74	80.00	80.00	22.00
Body temperature (°C)	70.00	36.45	36.30	36.60	36.50	36.40	14.00
Body weight (kg)	70.00	65.17	62.12	68.21	64.15	63.00	3.00

Table 44 Vital signs – descriptive statistics (day 0)

Day 0	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	66.00	100.00	72.00	84.00	44.00	12.00	85.17	9.23
Systolic pressure (mmHg)	100.00	170.00	120.00	135.00	70.00	16.00	181.08	13.82
Diastolic pressure (mmHg)	60.00	105.00	80.00	90.00	45.00	10.00	106.16	10.30
Body temperature (°C)	32.78	37.22	36.40	36.70	4.44	0.30	0.42	0.65
Body weight (kg)	41.00	124.50	55.20	72.50	83.50	17.30	163.23	12.78

Table 45 Vital signs – descriptive statistics (day 13)

Day 13	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	70.0	78.8	76.6	81.1	80.0	80.0	12.0
Systolic pressure (mmHg)	70.0	126.5	123.5	129.4	125.0	120.0	17.0
Diastolic pressure (mmHg)	70.0	83.8	81.5	86.0	84.5	80.0	20.0
Body temperature (°C)	70.0	36.5	36.4	36.7	36.6	36.4	12.0
Body weight (kg)	70.0	65.3	62.2	68.3	64.2	Multiple	

Equoral[®] capsules

Table 46 Vital signs – descriptive statistics (day 13)

Day 13	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	58.00	110.00	72.00	86.00	52.00	13.00	87.52	9.36
Systolic pressure (mmHg)	90.00	160.00	120.00	135.00	70.00	15.00	154.96	12.45
Diastolic pressure (mmHg)	50.00	105.00	80.00	90.00	56.00	10.00	89.77	9.47
Body temperature (°C)	32.78	38.33	38.40	38.76	5.58	0.38	0.37	0.61
Body weight (kg)	40.38	123.50	55.50	72.00	83.20	16.50	163.98	12.80

Table 47 Vital signs – descriptive statistics (day 14)

Day 14	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	68.0	78.1	75.8	80.5	80.0	72.0	7.0
Systolic pressure (mmHg)	68.0	127.2	123.8	130.5	128.5	130.0	14.0
Diastolic pressure (mmHg)	68.0	81.1	78.0	84.3	80.0	80.0	21.0
Body temperature (°C)	68.0	36.5	36.5	36.8	36.5	36.4	11.0
Body weight (kg)	68.0	65.1	62.0	68.2	64.0	58.0	4.0

Table 48 Vital signs – descriptive statistics (day 14)

Day 14	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	58.00	101.00	71.00	85.50	45.00	14.50	93.43	9.67
Systolic pressure (mmHg)	90.00	160.00	120.00	136.50	70.00	16.50	191.18	13.83
Diastolic pressure (mmHg)	20.00	106.00	80.00	90.00	66.00	10.00	172.04	13.12
Body temperature (°C)	35.00	37.22	36.40	36.79	2.22	0.39	0.11	0.33
Body weight (kg)	41.00	123.50	65.60	71.50	82.50	16.00	166.70	12.87

Table 48 Vital signs – descriptive statistics (day 15)

Day 15	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	70.00	79.44	77.40	81.48	80.00	80.00	9.00
Systolic pressure (mmHg)	70.00	125.80	122.57	129.03	126.50	120.00	14.00
Diastolic pressure (mmHg)	70.00	79.50	76.06	82.94	80.50	80.00	14.00
Body temperature (°C)	70.00	36.60	36.53	36.68	36.63	36.50	12.00
Body weight (kg)	70.00	65.35	62.31	68.39	64.10	58.00	3.00

Equoral® capsules

Table 49 Vital signs – descriptive statistics (day 15)

Day 15	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	60.00	100.00	72.00	86.00	40.00	14.00	73.67	8.58
Systolic pressure (mmHg)	90.00	160.00	120.00	135.00	70.00	15.00	183.23	13.54
Diastolic pressure (mmHg)	20.00	105.00	70.00	90.00	85.00	20.00	208.22	14.43
Body temperature (°C)	35.60	37.22	36.40	36.80	1.62	0.40	0.10	0.31
Body weight (kg)	41.20	124.50	58.50	72.00	83.30	15.50	162.89	12.76

Table 50 Vital signs – descriptive statistics (day 18)

Day 18	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	70.00	80.09	78.03	82.14	80.00	80.00	13.00
Systolic pressure (mmHg)	70.00	121.24	117.72	124.77	120.00	120.00	16.00
Diastolic pressure (mmHg)	70.00	77.99	74.65	81.32	80.00	80.00	19.00
Body temperature (°C)	70.00	41.25	31.92	50.58	36.80	36.40	15.00
Body weight (kg)	70.00	65.27	62.23	68.30	64.10	Multiple	

Table 51 Vital signs – descriptive statistics (day 18)

Day 18	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	62.00	104.00	73.00	84.00	42.00	11.00	74.34	8.62
Systolic pressure (mmHg)	88.00	150.00	110.00	130.00	62.00	20.00	218.48	14.78
Diastolic pressure (mmHg)	40.00	110.00	70.00	90.00	70.00	20.00	196.26	13.97
Body temperature (°C)	36.00	38.00	36.40	36.78	328.00	0.38	1531.62	39.14
Body weight (kg)	40.35	122.50	58.00	71.50	82.15	15.50	161.87	12.72

Table 52 Vital signs – descriptive statistics (day 21)

Day 21	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	67	80.40	78.41	82.39	80.00	80.00	11.00
Systolic pressure (mmHg)	67	124.55	121.58	127.54	125.00	Multiple	
Diastolic pressure (mmHg)	67	81.55	78.87	84.23	80.00	80.00	15.00
Body temperature (°C)	67	36.55	36.48	36.62	36.50	36.20	9.00
Body weight (kg)	67	65.39	62.28	68.51	64.20	Multiple	

Table 63 Vital signs – descriptive statistics (day 21)

Day 21	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	62.00	96.00	72.00	86.00	34.00	14.00	66.61	8.16
Systolic pressure (mmHg)	100.00	160.00	120.00	130.00	80.00	10.00	150.52	12.27
Diastolic pressure (mmHg)	50.00	106.00	72.00	90.00	58.00	18.00	120.49	10.98
Body temperature (°C)	36.00	37.22	36.30	36.72	1.22	0.42	0.09	0.30
Body weight (kg)	41.00	122.00	66.00	72.00	61.00	18.00	162.98	12.77

Table 64 Vital signs – descriptive statistics (day 27)

Day 27	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	70	77.76	75.58	79.94	80.00	80	10
Systolic pressure (mmHg)	70	122.21	119.01	125.41	120.00	120	18
Diastolic pressure (mmHg)	70	78.26	75.13	81.39	80.00	80	20
Body temperature (°C)	70	36.59	36.52	36.66	36.50	Multiple	
Body weight (kg)	70	65.38	62.34	68.42	64.00	64	4

Table 65 Vital signs – descriptive statistics (day 27)

Day 27	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	60.00	96.00	70.00	84.00	36.00	14.00	63.69	8.11
Systolic pressure (mmHg)	90.00	150.00	110.00	130.00	60.00	20.00	160.14	13.4
Diastolic pressure (mmHg)	40.00	106.00	70.00	90.00	65.00	20.00	172.45	13.1
Body temperature (°C)	36.00	37.50	36.40	36.78	1.50	0.36	0.09	0.3
Body weight (kg)	41.00	123.00	65.70	71.10	62.00	15.40	162.10	12.7

Table 66 Vital signs – descriptive statistics (day 28)

Day 28	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	67.0	77.7	75.6	79.8	80.0	Multiple	
Systolic pressure (mmHg)	67.0	121.4	118.5	124.4	120.0	110.0	16.0
Diastolic pressure (mmHg)	67.0	79.3	76.8	82.1	80.0	80.0	17.0
Body temperature (°C)	67.0	36.6	36.5	36.8	36.5	36.5	14.0
Body weight (kg)	67.0	64.9	62.0	67.9	64.0	64.0	4.0

Equoral[®] capsules

Table 57 Vital signs – descriptive statistics (day 28)

Day 28	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	56.00	85.00	71.00	84.00	39.00	13.00	72.87	8.54
Systolic pressure (mmHg)	90.00	150.00	110.00	130.00	60.00	20.00	146.86	12.12
Diastolic pressure (mmHg)	60.00	105.00	70.00	90.00	45.00	20.00	130.98	11.44
Body temperature (°C)	36.00	37.50	36.40	36.72	1.50	0.32	0.09	0.30
Body weight (kg)	41.00	123.50	55.50	71.00	82.50	15.50	146.37	12.11

Table 58 Vital signs – descriptive statistics (day 29)

Day 29	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	68.00	78.03	76.13	79.93	79.00	80.00	13.00
Systolic pressure (mmHg)	68.00	121.93	118.64	125.22	122.50	130.00	15.00
Diastolic pressure (mmHg)	68.00	79.69	78.60	82.57	80.00	80.00	11.00
Body temperature (°C)	68.00	36.45	36.15	36.75	36.63	36.50	13.00
Body weight (kg)	68.00	65.23	62.10	68.36	64.00	Multiple	

Table 59 Vital signs – descriptive statistics (day 29)

Day 29	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	60.00	99.00	71.00	82.00	39.00	11.00	61.85	7.86
Systolic pressure (mmHg)	90.00	150.00	110.00	130.00	60.00	20.00	164.76	13.50
Diastolic pressure (mmHg)	50.00	105.00	70.00	89.00	55.00	19.00	151.95	12.33
Body temperature (°C)	26.60	37.30	36.45	36.72	10.70	0.27	1.65	1.24
Body weight (kg)	41.00	123.00	55.50	72.40	82.00	16.90	167.56	12.89

Table 60 Vital signs – descriptive statistics (day 35)

Day 35	Valid N	Mean	Confidence interval for mean lower boundary	Confidence interval for mean upper boundary	Median	Mode	Frequency of mode
Radial pulse rate (bpm)	68.00	80.57	78.48	82.66	80.00	80.00	9.00
Systolic pressure (mmHg)	69.00	123.06	119.98	126.14	125.00	130.00	19.00
Diastolic pressure (mmHg)	69.00	80.58	77.99	83.17	80.00	80.00	19.00
Body temperature (°C)	68.00	36.62	36.55	36.69	36.60	36.50	12.00
Body weight (kg)	68.00	68.05	63.08	69.05	64.40	Multiple	

Equoral® capsules

Table 61 Vital signs – descriptive statistics (day 35)

Day 35	Minimum	Maximum	Lower	Upper	Range	Quartile	Variance	Standard deviation
Radial pulse rate (bpm)	64.00	100.00	73.00	87.00	36.00	14.00	74.52	8.63
Systolic pressure (mmHg)	88.00	160.00	120.00	130.00	72.00	10.00	164.50	12.82
Diastolic pressure (mmHg)	60.00	105.00	70.00	90.00	45.00	20.00	116.48	10.79
Body temperature (°C)	36.00	37.22	36.42	36.88	1.22	0.47	0.09	0.30
Body weight (kg)	42.00	123.20	57.00	72.65	81.20	15.65	153.11	12.37

14.3.7 Abnormal physical examination findings

Table 62 Abnormal findings in particular body system

	Count	Cumulative	Percent	Cumulative
General app.	10.00	10.00	4.41	4.41
Skin	9.00	19.00	3.96	8.37
E_E_N_T	101.00	120.00	44.49	52.86
Chest	1.00	121.00	0.44	53.30
Lungs	13.00	134.00	5.73	59.03
Heart	63.00	197.00	27.75	86.78
Abdomen	14.00	211.00	6.17	92.95
Extremities	16.00	227.00	7.05	100.00
Missing	0.00	227.00	0.00	100.00

Table 63 List of all abnormal findings

	Count	Cumulative	Percent	Cumulative
Not specified	7	7	3.00	3.00
Buffy	1	8	0.43	3.43
Plethoric	3	11	1.29	4.72
Acne	5	16	2.15	6.86
Echymosis over the right inguinal side	1	17	0.43	7.29
Warts	2	19	0.86	8.15
Gingival hypertrophy	10	29	4.29	12.44
Small ulceration (EENT)	1	30	0.43	12.87
Red conjunctivae	1	31	0.43	13.30
White tongue	39	70	16.74	30.04
No amygdala	1	71	0.43	30.47
Very obese	1	72	0.43	30.90
Diffuse wheezing	2	74	0.86	31.76
Rare wheezes	1	75	0.43	32.18
Systolic murmur	48	123	20.60	52.79
Distant heart sound	6	129	2.58	55.38
Spleen tip. scars	1	130	0.43	55.79
Enlargement of left kidney	2	132	0.86	56.65
Surgery on right side (abdomen)	1	133	0.43	57.08
Oedema (extremities)	8	141	3.43	60.51
Swelling (appearance)	1	142	0.43	60.94
Appearance of hairs (neck)	1	143	0.43	61.37
Injected conjunctivae	8	151	3.43	64.80
Bradycardia	1	152	0.43	65.23
Murmur over the graft	7	159	3.00	68.24
Poor or decreased air entry	9	168	3.86	72.10
Decreased peripheral pulse	3	171	1.29	73.39
Surgery (abdomen)	3	174	1.29	74.67
Echymosis over the right leg	1	175	0.43	75.10
Decreased heart sound	3	178	1.29	76.39
Oral thrush	38	216	16.31	92.70
Subicter sclera	1	217	0.43	93.13
Itching lesion	1	218	0.43	93.56
Herpes simplex	1	219	0.43	93.99
Bilateral crackles	1	220	0.43	94.42
Red right eye	2	222	0.86	95.27

Equoral[®] capsules

Rhonchi	1	223	0.43	95.70
Pale	2	225	0.88	98.58
Irregular sound (heart)	5	230	2.15	98.71
Wheezing	2	232	0.88	99.57
Traumatic haematoma over the graft	1	233	0.43	100.00
Missing	0	233	0.00	100.00

Table 64 List of individual abnormal findings (day -7, day 0, day 13)

	Subject No.	Day -7	Day 0	Day 13
General app.	3/1	Buffy	-	-
General app.	8/1	Plethoric	Plethoric	-
General app.	1/4	Not specified	Swelling	-
General app.	5/4	-	Appearance of hairs (neck)	-
Skin	1/1	Warts	Warts	-
Skin	12/1	Echymosis over the right inguinal side	-	-
Skin	1/4	Acne on back and face	Acne on back	-
Skin	5/4	Acne	Acne	-
EENT	2/1	-	Injected conjunctivae	Injected conjunctivae
EENT	3/1	Small ulceration	-	-
EENT	4/1	Red conjunctivae	White tongue	-
EENT	6/1	No amygdala	White tongue	-
EENT	7/1	White tongue	-	-
EENT	8/1	White tongue	White tongue	-
EENT	9/1	White tongue	-	-
EENT	14/1	Gingival hypertrophy	Gingival hypertrophy	Gingival hypertrophy
EENT	15/1	White tongue	-	-
EENT	16/1	White tongue	White tongue	-
Chest	3/1	Very obese	-	-
Lungs	4/1	Diffuse wheezing	Poor air entry, wheezing	Poor air entry
Lungs	8/1	Rare wheezes	-	-
Heart	3/1	Systolic murmur	Systolic murmur	Systolic murmur
Heart	4/1	Distant heart sound	-	No specified
Heart	6/1	Systolic murmur	Systolic murmur	-
Heart	7/1	Systolic murmur	-	Systolic murmur
Heart	9/1	-	-	Systolic murmur
Heart	12/1	Systolic murmur	Bradycardia	-
Heart	13/1	-	Systolic murmur	Systolic murmur
Abdomen	2/1	Spleen tip, scars	-	-
Abdomen	5/1	Enlargement of left kidney	-	-
Abdomen	13/1	-	Murmur over the graft	-
Abdomen	18/1	Surgery on right side	-	-
Extremities	3/1	-	Oedema	-
Extremities	4/1	Oedema, weak pulse	-	Not specified
Extremities	12/1	-	-	Decreased peripheral pulse

Table 65 List of individual abnormal findings (day 14, day 15, day 18)

	Subject No.	Day 14	Day 15	Day 18
General app.	3/1	-	-	-
General app.	8/1	-	-	Plethoric
General app.	1/4	-	-	-
General app.	5/4	-	-	-
Skin	1/1	-	-	-
Skin	12/1	-	-	-
Skin	1/4	-	-	-
Skin	5/4	-	-	-
EENT	2/1	Injected conjunctivae	Injected conjunctivae	-
EENT	3/1	-	-	-
EENT	4/1	-	-	-
EENT	6/1	-	-	-
EENT	7/1	-	-	-
EENT	8/1	-	-	Thrush
EENT	9/1	-	-	-
EENT	10/1	-	-	Subictar sclera
EENT	12/1	-	-	Thrush
EENT	14/1	Gingival hypertrophy	Gingival hypertrophy	Gingival hypertrophy
EENT	15/1	-	-	Thrush
EENT	16/1	-	-	Thrush
EENT	17/1	-	-	Thrush
Chest	3/1	-	-	-
Lungs	3/1	-	Decreased air entry	-
Lungs	4/1	Poor air entry	Poor air entry	Poor air entry
Lungs	8/1	-	-	-
Heart	3/1	-	-	Systolic murmur.
Heart	4/1	Decreased heart sound	Decreased heart sound	distant heart sound
Heart	5/1	Systolic murmur	-	Distant heart sound
Heart	6/1	-	-	-
Heart	7/1	Systolic murmur	Systolic murmur	Systolic murmur
Heart	9/1	-	-	-
Heart	10/1	-	-	Systolic murmur.
Heart	12/1	-	-	Irregular sound
Heart	13/1	Systolic murmur	Systolic murmur	Systolic murmur
Heart	15/1	-	-	Systolic murmur
Heart	17/1	-	-	Systolic murmur
Abdomen	2/1	-	-	-
Abdomen	5/1	-	-	-
Abdomen	13/1	-	-	-
Abdomen	18/1	Surgery	Surgery	-
Extremities	3/1	-	-	-
Extremities	4/1	Oedema	Not specified	-
Extremities	10/1	Ecchymosis over the right leg	-	-
Extremities	12/1	Decreased peripheral pulse	-	Oedema

Equoral® capsules

Table 66 List of individual abnormal findings (day 21, day 27, day 28)

	Subject No.	Day 21	Day 27	Day 28
General app.	3/1	-	-	-
General app.	8/1	-	-	-
General app.	1/4	Not specified	-	-
General app.	5/4	-	-	-
Skin	1/1	-	-	-
Skin	12/1	itching lesion	-	-
Skin	1/4	Acne on back	-	-
Skin	5/4	-	-	-
EENT	1/1	Thrush	Thrush	Thrush
EENT	2/1	Injected conjunctivae	Injected conjunctivae	Injected conjunctivae
EENT	3/1	White tongue	-	White tongue
EENT	4/1	-	-	-
EENT	5/1	-	Thrush	Thrush
EENT	6/1	Thrush	Red right eye	Red right eye
EENT	7/1	White tongue	White tongue	Thrush
		Herpes simplex.	White tongue	White tongue
EENT	8/1	white tongue	-	-
EENT	9/1	Thrush	Thrush	Thrush
EENT	10/1	-	-	-
EENT	11/1	Thrush	Thrush	Thrush
EENT	12/1	Thrush	-	White tongue
EENT	13/1	White tongue	-	White tongue
EENT	14/1	Thrush	-	Gingival hypertrophy
EENT	15/1	Thrush	Thrush	Thrush
EENT	16/1	Thrush	White tongue	Thrush
EENT	17/1	Thrush	Thrush	White tongue
Chest	3/1	-	-	-
Lungs	3/1	-	-	-
		Wheezing, bilateral crackles	-	-
Lungs	4/1	-	Poor air entry, rhonchi	Poor air entry
Lungs	8/1	-	-	-
Heart	1/1	Systolic murmur	Systolic murmur	Systolic murmur
Heart	3/1	-	-	-
Heart	4/1	Distant heart sound	Decreased heart sound	Not specified
Heart	5/1	Irregular heart sound	Systolic murmur	Systolic murmur
Heart	6/1	Systolic murmur	Systolic murmur	Systolic murmur
Heart	7/1	-	-	-
Heart	8/1	-	-	-
Heart	10/1	Irregular heart sound	-	-
Heart	12/1	-	-	-
Heart	13/1	-	Systolic murmur	Systolic murmur
Heart	14/1	-	Systolic murmur	Systolic murmur
Heart	15/1	Systolic murmur	Systolic murmur	Systolic murmur
Heart	16/1	-	Systolic murmur	-
Heart	17/1	-	-	-
Abdomen	2/1	-	-	-
		-	Enlargement of left kidney	-
Abdomen	5/1	-	-	-
Abdomen	13/1	-	-	Murmur over the graft
Abdomen	15/1	-	Murmur over the graft	Murmur over the graft
Abdomen	18/1	Surgery	-	-
Extremities	3/1	-	-	-

Equoral® capsules

Extremities	4/1	Oedema	Decreased peripheral pulse	Not specified
Extremities	10/1	-	-	-
Extremities	12/1	-	-	-

Table 67 List of individual abnormal findings (day 29, day 35)

	Subject No.	Day 29	Day 35
General app.	3/1	-	-
General app.	8/1	-	-
General app.	15/1	Pale	Pale
General app.	1/4	-	-
General app.	5/4	-	-
Skin	1/1	-	-
Skin	12/1	-	-
Skin	1/4	-	-
Skin	5/4	-	-
EENT	1/1	Thrush	Thrush
EENT	2/1	Injected conjunctivae	-
EENT	3/1	White tongue	White tongue
EENT	4/1	-	White tongue
EENT	5/1	Thrush	Thrush
EENT	6/1	White tongue	White tongue
EENT	7/1	-	-
EENT	8/1	White tongue	White tongue
EENT	9/1	Thrush	Thrush
EENT	10/1	White tongue	White tongue
EENT	11/1	-	Thrush
EENT	12/1	White tongue	White tongue
EENT	13/1	Thrush	White tongue
EENT	14/1	Gingival hypertrophy	Gingival hypertrophy.
EENT	15/1	Thrush	white tongue
EENT	16/1	White tongue	Thrush
EENT	17/1	Thrush	White tongue
Chest	3/1	-	-
Lungs	3/1	-	-
Lungs	4/1	Poor air entry	Wheezing
Lungs	8/1	-	-
Heart	1/1	-	-
Heart	3/1	-	-
Heart	4/1	Distant heart sound	Distant heart sound
Heart	5/1	Systolic murmur	Irregular systolic murmur
Heart	6/1	Systolic murmur	Systolic murmur
Heart	7/1	Systolic murmur	-
Heart	8/1	Systolic murmur	-
Heart	9/1	-	-
Heart	10/1	-	Irregular heart sound
Heart	12/1	-	-
Heart	13/1	-	-
Heart	14/1	-	-
Heart	15/1	-	Systolic murmur

Equoral® capsules

Heart	16/1	-	-
Heart	17/1	-	-
Abdomen	2/1	-	-
Abdomen	5/1	-	-
Abdomen	13/1	Murmur over the graft	-
Abdomen	15/1	Murmur over the graft	Murmur over the graft
Abdomen	18/1	-	-
			Traumatic haematoma over graft
Extremities	3/1	-	Oedema
Extremities	4/1	Oedema	Oedema
Extremities	10/1	-	-
Extremities	12/1	-	-

Table 68 Summary table – abnormal findings

	Count											
	D-7	D-0	D-13	D-14	D-15	D-18	D-21	D-27	D-28	D-29	D-35	
Not specified:	1		2		1		1		2			
Buffy	1											
Plethoric	1	1				1						
Swelling		1										
Pale										1	1	
Appearance of hairs (neck)		1										
Itching lesion							1					
Acne	2	2					1					
Echymosis over the right inguinal side	1											
Warts	1	1										
Gingival hypertrophy	1	1	1	1	1	1		1	1	1	1	
Small ulceration	1											
Red conjunctivae	1											
Red right eye								1	1			
Injected conjunctivae		1	1	1	1		1	1	1	1		
Herpes simplex							1					
White tongue	5	4					4	5	5	7	10	
Thrush						5	9	6	7	6	5	
No amygdalae	1					1						
Subicteric sclera												
Very obese	1											
Poor or decreased air entry		1	1	1	1	1		1	1	1		
Rhonchi								1				
Wheezing		1					1				1	
Bilateral crackles							1					
Diffuse wheezing	1											
Rare wheezes	1											
Bradycardia		1										
Systolic murmur	4	3	4	4	3	7	3	7	6	4	3	
Distant heart sound	1					2	1			1	1	
Decreased heart sound				1	1			1				
Irregular heart sound						1	2			1	1	

Equoral® capsules

Spleen tip, scars	1											
Enlargement of left kidney	1							1				
Murmur over the graft		1						1	1	1	1	
Surgery on right side	1						1					
Surgery (abdomen)				1	1							
Oedema	1	2		1		1	1			1	1	
Decreased peripheral pulse			1	1				1				
Echymosis over the right leg				1								
Missing	0	0	0	0	0	0	0	0	0	0	0	0

Table 69 List of abnormal findings: Day -7

Day -7	Subject No.	Centre No.
General app.	1	4 Not specified
General app.	3	1 Buffy
General app.	8	1 Plethoric
Skin	1	4 Acne on back and face
Skin	5	4 Acne
Skin	12	1 Echymosis over the right inguinal side
Skin	1	1 Warts
EENT	14	1 Gingival hypertrophy
EENT	3	1 Small ulceration
EENT	4	1 Red conjunctivae
EENT	7	1 White tongue
EENT	8	1 White tongue
EENT	9	1 White tongue
EENT	15	1 White tongue
EENT	16	1 White tongue
EENT	6	1 No amygdala
Chest	3	1 Very obese
Lungs	4	1 Diffuse wheezing
Lungs	8	1 Rare wheezes
Heart	12	1 Systolic murmur
Heart	3	1 Systolic murmur
Heart	4	1 Distant heart sound
Heart	6	1 Systolic murmur
Heart	7	1 Systolic murmur
Abdomen	2	1 Spleen tip, scars
Abdomen	5	1 Enlargement of left kidney
Abdomen	18	1 Surgery on right side
Extremities	4	1 Oedema, weak pulse

Equoral[®] capsules

Table 70 Summary table — abnormal findings: Day -7

Day -7	Count	Cumulative	Percent	Cumulative
Not specified	1.00	1.00	3.57	3.57
Buffy	1.00	2.00	3.57	7.14
Plethoric	1.00	3.00	3.57	10.71
Acne on back and face	1.00	4.00	3.57	14.29
Acne	1.00	5.00	3.57	17.86
Ecchymosis over the right inguinal side	1.00	6.00	3.57	21.43
Warts	1.00	7.00	3.57	25.00
Gingival hypertrophy	1.00	8.00	3.57	28.57
Small ulceration	1.00	9.00	3.57	32.14
Red conjunctivae	1.00	10.00	3.57	35.71
White tongue	5.00	15.00	17.86	53.57
No amygdala	1.00	16.00	3.57	57.14
Very obese	1.00	17.00	3.57	60.71
Diffuse wheezing	1.00	18.00	3.57	64.29
Rare wheezes	1.00	19.00	3.57	67.86
Systolic murmur	4.00	23.00	14.29	82.14
Distant heart sound	1.00	24.00	3.57	85.71
Spleen tip, scars	1.00	25.00	3.57	89.29
Enlargement of left kidney	1.00	26.00	3.57	92.86
Surgery on right side	1.00	27.00	3.57	96.43
Oedema, weak pulse	1.00	28.00	3.57	100.00
Missing	0.00	28.00	0.00	100.00

Table 71 List of abnormal findings: Day 0

Day 0	Subject No.	Centrino
General app.	1	4 Swelling Appearance of hairs
General app.	5	4 (neck)
General app.	8	1 Plethoric
Skin	1	4 Acne on back
Skin	5	4 Acne
Skin	1	1 Warts
EENT	14	1 Gingival hypertrophy
EENT	2	1 Injected conjunctivae
EENT	4	1 White tongue
EENT	6	1 White tongue
EENT	8	1 White tongue
EENT	16	1 White tongue
Lungs	4	1 Poor air entry, wheezing
Heart	12	1 Bradycardia
Heart	13	1 Systolic murmur
Heart	3	1 Systolic murmur
Heart	6	1 Systolic murmur
Abdomen	13	1 Murmur over the graft
Extremities	3	1 Oedema
Extremities	4	1 Oedema (pitting)

Equoral® capsules

Table 72 Summary table – abnormal findings: Day 0

Day 0	Count	Cumulative	Percent	Cumulative
Plethoric	1.00	1.00	5.00	5.00
Warts	1.00	2.00	5.00	10.00
White tongue	4.00	6.00	20.00	30.00
Systolic murmur	3.00	9.00	15.00	45.00
Swelling	1.00	10.00	5.00	50.00
Appearance of hairs (neck)	1.00	11.00	5.00	55.00
Acne on back	1.00	12.00	5.00	60.00
Acne	1.00	13.00	5.00	65.00
Gingival hypertrophy	1.00	14.00	5.00	70.00
Injected conjunctivae	1.00	15.00	5.00	75.00
Poor air entry, wheezing	1.00	16.00	5.00	80.00
Bradycardia	1.00	17.00	5.00	85.00
Murmur over the graft	1.00	18.00	5.00	90.00
Oedema	1.00	19.00	5.00	95.00
Oedema (pitting)	1.00	20.00	5.00	100.00
Missing	0.00	20.00	0.00	100.00

Table 73 List of abnormal findings: Day 13

Day 13	Subject No.	Count No.
E_E_N_T	14	1 Gingival hypertrophy
E_E_N_T	2	1 Injected conjunctivae
Lungs	4	1 Poor air entry
Heart	13	1 Systolic murmur
Heart	3	1 Systolic murmur
Heart	4	1 Not specified
Heart	7	1 Systolic murmur
Heart	9	1 Systolic murmur
Extremities	12	1 Decreased peripheral pulse
Extremities	4	1 Not specified

Table 74 Summary tables – abnormal findings: Day 13

Day 13	Count	Cumulative	Percent	Cumulative
Not specified	2.00	2.00	20.00	20.00
Gingival hypertrophy	1.00	3.00	10.00	30.00
Systolic murmur	4.00	7.00	40.00	70.00
Injected conjunctivae	1.00	8.00	10.00	80.00
Poor air entry	1.00	9.00	10.00	90.00
Decreased peripheral pulse	1.00	10.00	10.00	100.00
Missing	0.00	10.00	0.00	100.00

Equoral® capsules

Table 75 List of abnormal findings: Day 14

Day 14	Subject No.	Centre No.	
E_E_N_T	14	1	Gingival hypertrophy
E_E_N_T	2	1	Injected conjunctivae
Lungs	4	1	Poor air entry
Heart	13	1	Systolic murmur
Heart	3	1	Systolic murmur
Heart	4	1	Decreased heart sound
Heart	5	1	Systolic murmur
Heart	7	1	Systolic murmur
Abdomen	18	1	Surgery
Extremities	12	1	Decreased peripheral pulse
Extremities	4	1	Oedema
Extremities	10	1	Ecchymosis over right leg

Table 76 Summary tables -- abnormal findings: Day 14

Day 14	Count	Cumulative	Percent	Cumulative
Gingival hypertrophy	1.00	1.00	8.33	8.33
Systolic murmur	4.00	5.00	33.33	41.67
Injected conjunctivae	1.00	6.00	8.33	50.00
Poor air entry	1.00	7.00	8.33	58.33
Decreased heart sound	1.00	8.00	8.33	66.67
Surgery	1.00	9.00	8.33	75.00
Decreased peripheral pulse	1.00	10.00	8.33	83.33
Oedema	1.00	11.00	8.33	91.67
Ecchymosis over right leg	1.00	12.00	8.33	100.00
Missing	0.00	12.00	0.00	100.00

Table 77 List of abnormal findings: Day 15

Day 15	Subject No.	Centre No.	
E_E_N_T	14	1	Gingival hypertrophy
E_E_N_T	2	1	Injected conjunctivae
Lungs	3	1	Decreased air entry
Lungs	4	1	Poor air entry
Heart	13	1	Systolic murmur
Heart	3	1	Systolic murmur
Heart	4	1	Decreased heart sound
Heart	7	1	Systolic murmur
Abdomen	18	1	Surgery
Extremities	4	1	Not specified

Equoral® capsules

Table 78 Summary tables - abnormal findings: Day 15

Day 15	Count	Cumulative	Percent	Cumulative
Not specified	1.00	1.00	10.00	10.00
Gingival hypertrophy	1.00	2.00	10.00	20.00
Systolic murmur	3.00	5.00	30.00	50.00
Injected conjunctivae	1.00	6.00	10.00	60.00
Poor air entry	1.00	7.00	10.00	70.00
Surgery	1.00	8.00	10.00	80.00
Decreased air entry	1.00	9.00	10.00	90.00
Decreased heart sound	1.00	10.00	10.00	100.00
Missing	0.00	10.00	0.00	100.00

Table 79 List of abnormal findings: Day 18

Day 18	Subject No.	Centra No.
General app.	8	1 Plethoric
EENT	12	1 Thrush
EENT	14	1 Gingival hypertrophy
EENT	8	1 Thrush
EENT	10	1 Subictar sclera
EENT	15	1 Thrush
EENT	16	1 Thrush
EENT	17	1 Thrush
Lungs	4	1 Poor air entry
Heart	12	1 Systolic murmur
Heart	13	1 Systolic murmur
Heart	3	1 Systolic murmur + distant heart sound
Heart	4	1 Distant heart sound
Heart	7	1 Systolic murmur
Heart	10	1 Systolic murmur + irregular sound
Heart	15	1 Systolic murmur
Heart	17	1 Systolic murmur
Extremities	12	1 Oedema

Table 80 Summary tables - abnormal findings: Day 18

Day 18	Count	Cumulative	Percent	Cumulative
Plethoric	1.00	1.00	5.56	5.56
Gingival hypertrophy	1.00	2.00	5.56	11.11
Systolic murmur	5.00	7.00	27.78	38.89
Distant heart sound	1.00	8.00	5.56	44.44
Poor air entry	1.00	9.00	5.56	50.00
Thrush	5.00	14.00	27.78	77.78
Subictar sclera	1.00	15.00	5.56	83.33
Systolic murmur + distant heart sound	1.00	16.00	5.56	88.89
Systolic murmur + irregular sound	1.00	17.00	5.56	94.44
Oedema	1.00	18.00	5.56	100.00
Missing	0.00	18.00	0.00	100.00

Equoral® capsules

Table 81 List of abnormal findings: Day 21

Day 21	Subject No.	Center No.	
General app.	1	4	Not specified
Skin	1	4	Acne on back
Skin	12	1	itching lesion
EENT	12	1	Thrush
EENT	13	1	White tongue
EENT	14	1	Thrush
EENT	1	1	Thrush
EENT	2	1	Injected conjunctivae
EENT	3	1	White tongue
EENT	6	1	Thrush
EENT	7	1	White tongue
EENT	8	1	Herpes simplex + white tongue
EENT	9	1	Thrush
EENT	15	1	Thrush
EENT	16	1	Thrush
EENT	17	1	Thrush
EENT	11	1	Thrush
Lungs	4	1	Wheezing, bilateral crackles
Heart	1	1	Systolic murmur
Heart	4	1	Distant heart sound
Heart	5	1	Irregular heart sound
Heart	6	1	Systolic murmur
Heart	10	1	Irregular heart sound
Heart	15	1	Systolic murmur
Abdomen	18	1	Surgery
Extremities	4	1	Oedema

Table 82 Summary tables - abnormal findings: Day 21

Day 21	Count	Cumulative	Percent	Cumulative
Not specified	1.00	1.00	3.85	3.85
White tongue	3.00	4.00	11.54	15.38
Systolic murmur	3.00	7.00	11.54	26.92
Distant heart sound	1.00	8.00	3.85	30.77
Injected conjunctivae	1.00	9.00	3.85	34.62
Surgery	1.00	10.00	3.85	38.46
Thrush	9.00	19.00	34.62	73.08
Acne on back	1.00	20.00	3.85	76.92
itching lesion	1.00	21.00	3.85	80.77
Herpes simplex + white tongue	1.00	22.00	3.85	84.62
Wheezing, bilateral crackles	1.00	23.00	3.85	88.46
Irregular heart sound	2.00	25.00	7.69	96.15
Oedema	1.00	26.00	3.85	100.00
Missing	0.00	26.00	0.00	100.00

Table 83 List of abnormal findings: Day 27

Day 27	Subject No.	Centre No.	
EENT	12	1	White tongue
EENT	13	1	White tongue
EENT	14	1	Gingival hypertrophy
EENT	1	1	Thrush
EENT	2	1	Injected conjunctivae
EENT	5	1	Thrush
EENT	6	1	Red right eye
EENT	7	1	White tongue
EENT	8	1	White tongue
EENT	9	1	Thrush
EENT	15	1	Thrush
EENT	16	1	White tongue
EENT	17	1	Thrush
EENT	11	1	Thrush
Lungs	4	1	Poor air entry, rhonchi
Heart	13	1	Systolic murmur
Heart	14	1	Systolic murmur
Heart	1	1	Systolic murmur
Heart	4	1	Decreased heart sound
Heart	5	1	Systolic murmur
Heart	6	1	Systolic murmur
Heart	15	1	Systolic murmur
Heart	16	1	Systolic murmur
Abdomen	5	1	Left enlarged kidney
Abdomen	15	1	Murmur over the graft
Extremities	4	1	Decreased peripheral pulse

Table 84 Summary tables - abnormal findings: Day 27

Day 27	Count	Cumulative	Percent	Cumulative
Gingival hypertrophy	1.00	1.00	3.85	3.85
White tongue	5.00	6.00	19.23	23.08
Systolic murmur	7.00	13.00	26.92	50.00
Injected conjunctivae	1.00	14.00	3.85	53.85
Decreased heart sound	1.00	15.00	3.85	57.69
Thrush	6.00	21.00	23.08	80.77
Red right eye	1.00	22.00	3.85	84.62
Poor air entry, rhonchi	1.00	23.00	3.85	88.46
Left enlarged kidney	1.00	24.00	3.85	92.31
Murmur over the graft	1.00	25.00	3.85	96.15
Decrease peripheral pulse	1.00	26.00	3.85	100.00
Missing	0.00	26.00	0.00	100.00

Equoral® capsules

Table 85 List of abnormal findings: Day 28

Day 28	Subject No.	Centre No.
EENT	12	1 White tongue
EENT	13	1 White tongue
EENT	14	1 Gingival hypertrophy
EENT	1	1 Thrush
EENT	2	1 Injected conjunctivae
EENT	3	1 White tongue
EENT	5	1 Thrush
EENT	6	1 Red right eye
EENT	7	1 Thrush
EENT	8	1 White tongue
EENT	9	1 Thrush
EENT	15	1 Thrush
EENT	16	1 Thrush
EENT	17	1 White tongue
EENT	11	1 Thrush
Lungs	4	1 Poor air entry
Heart	14	1 Systolic murmur
Heart	1	1 Systolic murmur
Heart	4	1 Not specified
Heart	5	1 Systolic murmur
Heart	6	1 Systolic murmur
Heart	13	1 Systolic murmur
Heart	15	1 Systolic murmur
Abdomen	13	1 Murmur over the graft
Abdomen	15	1 Murmur over the graft
Extremities	4	1 Not specified

Table 86 Summary tables - abnormal findings: Day 28

Day 28	Count	Cumulative	Percent	Cumulative
Not specified	2.00	2.00	7.69	7.69
Gingival hypertrophy	1.00	3.00	3.85	11.54
White tongue	5.00	8.00	19.23	30.77
Systolic murmur	6.00	14.00	23.08	53.85
Injected conjunctivae	1.00	15.00	3.85	57.69
Poor air entry	1.00	16.00	3.85	61.54
Thrush	7.00	23.00	26.92	88.46
Murmur over the graft	2.00	25.00	7.69	96.15
Red right eye	1.00	26.00	3.85	100.00
Missing	0.00	26.00	0.00	100.00

Equoral[®] capsules

Table 87 List of abnormal findings: Day 29

Day 29	Subject No.	Centre No.	
General app.	15	1	Pale
EENT	12	1	White tongue
EENT	13	1	Thrush
EENT	14	1	Gingival hypertrophy
EENT	1	1	Thrush
EENT	2	1	Injected conjunctivae
EENT	3	1	White tongue
EENT	5	1	Thrush
EENT	6	1	White tongue
EENT	8	1	White tongue
EENT	9	1	Thrush
EENT	10	1	White tongue
EENT	15	1	Thrush
EENT	16	1	White tongue
EENT	17	1	White tongue
EENT	11	1	Thrush
Lungs	4	1	Poor air entry
Heart	4	1	Distant heart sound
Heart	5	1	Systolic murmur
Heart	6	1	Systolic murmur
Heart	7	1	Systolic murmur
Heart	8	1	Systolic murmur
Heart	10	1	Irregular sound
Abdomen	13	1	Murmur over the graft
Abdomen	15	1	Murmur over the graft
Extremities	4	1	Oedema

Table 88 Summary tables - abnormal findings: Day 29

Day 29	Count	Cumulative	Percent	Cumulative
Gingival hypertrophy	1.00	1.00	3.85	3.85
White tongue	7.00	8.00	26.92	30.77
Systolic murmur	4.00	12.00	15.38	46.15
Distant heart sound	1.00	13.00	3.85	50.00
Injected conjunctivae	1.00	14.00	3.85	53.85
Poor air entry	1.00	15.00	3.85	57.69
Thrush	6.00	21.00	23.08	80.77
Oedema	1.00	22.00	3.85	84.62
Pale	1.00	23.00	3.85	88.46
Irregular sound	1.00	24.00	3.85	92.31
Murmur over the graft	2.00	26.00	7.69	100.00
Missing	0.00	26.00	0.00	100.00

Table 89 List of abnormal findings: Day 35

Day 35	Subject No.	Centre No.	
General app.	15	1	Pale
EENT	12	1	White tongue
EENT	13	1	White tongue
EENT	14	1	Gingival hypertrophy + white tongue
EENT	1	1	Thrush
EENT	3	1	White tongue
EENT	4	1	White tongue
EENT	5	1	Thrush
EENT	6	1	White tongue
EENT	8	1	White tongue
EENT	9	1	Thrush
EENT	10	1	White tongue
EENT	15	1	Thrush
EENT	16	1	White tongue
EENT	17	1	White tongue
EENT	11	1	Thrush
Lungs	4	1	Wheezing
Heart	4	1	Distant heart sound
Heart	5	1	Irregular systolic murmur
Heart	6	1	Systolic murmur
Heart	10	1	Irregular heart sound
Heart	15	1	Systolic murmur
Abdomen	15	1	Murmur over the graft
Extremities	3	1	Traumatic haematoma over the graft
Extremities	4	1	Oedema

Table 90 Summary tables - abnormal findings: Day 35

Day 35	Count	Cumulative	Percent	Cumulative
White tongue	9.00	9.00	36.00	36.00
Systolic murmur	2.00	11.00	8.00	44.00
Distant heart sound	1.00	12.00	4.00	48.00
Murmur over the graft	1.00	13.00	4.00	52.00
Thrush	5.00	18.00	20.00	72.00
Oedema	1.00	19.00	4.00	76.00
Irregular heart sound	1.00	20.00	4.00	80.00
Pale	1.00	21.00	4.00	84.00
Gingival hypertrophy + white tongue	1.00	22.00	4.00	88.00
Wheezing	1.00	23.00	4.00	92.00
Irregular systolic murmur	1.00	24.00	4.00	96.00
Traumatic haematoma over the graft	1.00	25.00	4.00	100.00
Missing	0.00	25.00	0.00	100.00

15 REFERENCES

1. Karch, Casagna. Definition of Relationship to study treatment. J. Am. Med. Assoc. 1975; 234:1226-1241
2. Loo CS, Morad Z, Lim TO et al: A randomized, controlled trial to assess the safety of switching stable renal transplant patients from Sandimmun to Sandimmun Neoral. Transplant Proc 1996; 28(3); 1328.
3. Tsang WK, Ho YW, Tong KL et al: Safety, tolerability, and pharmacokinetics of Sandimmun Neoral: conversion study in stable renal transplant recipients. Transplant Proc 1996; 28(3):1330.
4. Shah MB, Martin JE, Schroeder TJ et al: The evaluation of the safety and tolerability of the two formulations of cyclosporine: Neoral and Sandimmune. A meta-analysis. Transplantation 1999; 67(11):1411.
5. Roza A, Tomianovich S, Merion R: Conversion of stable renal allograft recipients to a bioequivalent cyclosporine formulation. Transplantation 2002; 74(7):1013-17.

16. Appendices

16. Appendices**16.1 Study Information****16.1.1 Protocol and Protocol Amendments**

Protocol

Neoral® capsules/ Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase

TITLE PAGE

**A PHARMACOKINETIC CONVERSION STUDY OF
EQUORAL (IVAX-CR) AND NEORAL® IN STABLE
ADULT RENAL TRANSPLANT RECIPIENTS**

Study No.: 53/EQ/01/PK

Status: 25th February 2002 **FINAL VERSION**

Test Drug: Equoral capsules

PRINCIPAL INVESTIGATORS:

Professor Marwan Masri

Signature _____ Date: _____

Professor Gaby Kamel

Signature _____ Date: _____

Professor Rasahd Barsoum

Signature _____ Date: _____

Professor Mehmet Haberal

Signature _____ Date: _____

Professor Ahad J. Ghods

Signature _____ Date: _____

Professor Syed Adibul Rizivi

Signature _____ Date: _____

SPONSOR:

Ass. Prof. Vojtěch Kamarád MD, DSc.

Signature _____ Date: _____

The signature of the Principal Investigator and Sponsor's representative above indicates their approval of this Protocol.

Emergencies or Serious Adverse Event Refer safety section of the Protocol to page contact:

Study SAE Monitor's Name and Title

Office Telephone
No.:
e-mail:

Fax
No.:

24 Hour Emergency No.:

IVAX-CR
Czech Republic

CONFIDENTIALITY STATEMENT

This document contains trade secrets and proprietary information of IVAX-CR that IVAX-CR considers being confidential and that are subject to a confidentiality agreement entered into with IVAX-CR. Neither this document nor the information contained herein may be used or disclosed to others without the express written permission of IVAX-CR.

Neoral® capsules/ Equoral capsules

Study No.: 53/EQ/01/PK
CT Phase:

TITLE PAGE



Study No.: 53/EQ/01/PK

Status: 25th February 2002 **FINAL VERSION**

Test Drug: Equoral capsules

PRINCIPAL INVESTIGATORS:

Professor Marwan Masri

Signature [Signature] Date: 20/4/2002

Professor Gaby Knapel

Signature _____ Date: _____

Professor Rasad Baroun

Signature _____ Date: _____

Professor Mehmet Haberal

Signature _____ Date: _____

Professor Walid Al Khayal

Signature _____ Date: _____

Professor Syed Adilul Rizvi

Signature _____ Date: _____

SPONSOR:

Ass. Prof. Vojtěch Kameš MD, DSc.

Signature _____ Date: _____

The signature of the Principal Investigator and Sponsor's representative above indicates their approval of this Protocol.

Adverse Event Refer safety section of the Protocol to page contact:			
Study SAE Monitor's Name and Title	Office Telephone No.:	Fax No.:	
	e-mail:		

IVAX-CR
Czech Republic

CONFIDENTIALITY STATEMENT

This document contains trade secrets and proprietary information of IVAX-CR that IVAX-CR considers being confidential and that are subject to a confidentiality agreement entered into with IVAX-CR. Neither this document nor the information contained herein may be used or disclosed to others without the express written permission of IVAX-CR.

Form : PYS

PHONE NO. : 951 1 372 259

Document - approved signed copy/ok

Sign. No. 15073000K
17/1/02

TITLE PAGE



Study No: 530/Q01/PK

Start: 25th February 2002 **FINAL VERSION**

Yeni Deneyi: Kapsamlı raporlar

PRINCIPAL INVESTIGATORS:

Professor Marwan Masri

Signature *[Signature]* Date: 2002/20/4

Professor Gaby Kameel

Signature _____ Date: _____

Professor Hamed Hattoum

Signature _____ Date: _____

Professor Mohamed Hattoum

Signature *[Signature]* Date: April 12, 2002

Professor Ahmad J. Ghannam

Signature _____ Date: _____

Professor Syed Adilul Rizvi

Signature _____ Date: _____

SPONSOR:

Ass. Prof. Vojtech Krmakovic MD, DSc.

Signature _____ Date: _____

The signature of the Principal Investigator and Sponsor's representative above indicates their approval of this Protocol.

Emergency/Adverse Event Referral Refer safety action of the Protocol to page contact:			
Study SAP Monitor's Name and Title	Office Telephone No:	Fax No:	
	e-mail:		

IVAX-CR
Czech Republic

(CONFIDENTIALITY STATEMENT)

This document contains trade secrets and proprietary information of IVAX-CR that IVAX-CR considers being confidential and that are subject to a confidentiality agreement entered into with IVAX-CR. Neither this document nor the information contained herein may be used or disclosed to others without the express written permission of IVAX-CR.

PHONE NO. : 961 1 372 259

Apr. 09 2002 10:57AM P02

Neurobiological Research/Neurological Research

Study No. 53/EC/01/PK
011134.00

TITLE PAGE



Study No.: 53/EC/01/PK

Status: 25th February 2002 FINAL VERSION

Test Drug: Equival capsules

PRINCIPAL INVESTIGATORS:

Professor Marietta Mianari

Signature: *[Signature]* Date: 2002/20/4

Professor Gaby Kaniel

Signature: *[Signature]* Date: 19/4/02

Professor Rashed Harsmani

Signature: _____ Date: _____

Professor Michael Hahnel

Signature: _____ Date: _____

Professor Ahmad I. Ghods

Signature: _____ Date: _____

Professor Syed Adilul Rizvi

Signature: _____ Date: _____

SPONSOR:

Asst. Prof. Vojtěch Kamarád MD, DSc.

Signature: _____ Date: _____

The signature of the Principal Investigator and Sponsor's representative above indicates their approval of this Protocol.

Adverse Event Refer safety section of the Protocol to page contact:			
Study Site Monitor's Name and Title	Office Telephone No. or e-mail	Fax	No.

IVAX-CR
Czech Republic

CONFIDENTIALITY STATEMENT

This document contains trade secrets and proprietary information of IVAX-CR that IVAX-CR considers being confidential and that are subject to a confidentiality agreement entered into with IVAX-CR. Neither this document nor the information contained herein may be used or disclosed to others without the express written permission of IVAX-CR.

Study No.: 53/EQ/01/PK

Status: 25th February 2002 **FINAL VERSION**

Test Drug: Equoral capsules

PRINCIPAL INVESTIGATORS:

Professor Marwan Masri

Signature [Signature] Date: 20/4/2002

Professor Gaby Kamel

Signature _____ Date: _____

Professor Rasahd Barsonm

Signature _____ Date: _____

Professor Mehmet Haberal

Signature _____ Date: _____

Professor Ahmad J. Ghods

Signature _____ Date: _____

Professor Syed Adibul Rizvi

Signature [Signature] Date: 17th APRIL '2002**SPONSOR:**

Ass. Prof. Vojtěch Kamarád MD, DSc.

Signature _____ Date: _____

The signature of the Principal Investigator and Sponsor's representative above indicates their approval of this Protocol.

Emergencies or Serious Adverse Event Refer safety section of the Protocol to page contact:

Study SAE Monitor's Name and Title

Office Telephone No: 92-21-9215752/921578

Fax No: 92-21-9215469/9215362

24 Hour Emergency No.:

Email: slutpk@sat.net.pk

IVAX-CR
Czech Republic

CONFIDENTIALITY STATEMENT

This document contains trade secrets and proprietary information of IVAX-CR that IVAX-CR considers being confidential and that are subject to a confidentiality agreement entered into with IVAX-CR. Neither this document nor the information contained herein may be used or disclosed to others without the express written permission of IVAX-CR.

The Cairo Kidney FAX

PHONE NO. : 5769749

Apr. 09 2002 10:03PM

Neoral® capsules/ Equoral capsules

Study No.: 53/EQ/01/PK
CT I, phase

TITLE PAGE

A PHARMACOKINETIC CONVERSION STUDY OF EQUORAL (IVAX-CR) AND NEORAL IN STABLE ADULT RENAL TRANSPLANT RECIPIENTS

Study No.: 53/EQ/01/PK

Status: 25th February 2002 **FINAL VERSION**

Test Drug: Equoral capsules

PRINCIPAL INVESTIGATORS:

Professor Marwan Minsal

Signature Marwan Minsal Date: 20/4/2002

Professor Gaby Kameel

Signature _____ Date: _____

Professor Rashed Barsoum

Signature R. Barsoum Date: 4/4/2002

Professor Mohamed Haberal

Signature _____ Date: _____

Professor Ahmad J. Gheda

Signature _____ Date: _____

Professor Syed Adilul Rabi

Signature _____ Date: _____

SPONSOR:

Ass. Prof. Vojtěch Kaniarad MD, DSc.

Signature _____ Date: _____

The signature of the Principal Investigator and Sponsor's representative above indicates their approval of this Protocol.

Endogenous Safety Adverse Event Refer safety section of the Protocol to page contact:			
Study SAE Monitor's Name and Title	Office Telephone	Fax	No.
	No.:		
	e-mail:		

 IVAX-CR
 Czech Republic

CONFIDENTIALITY STATEMENT

This document contains trade secrets and proprietary information of IVAX-CR that IVAX-CR considers being confidential and that are subject to a confidentiality agreement entered into with IVAX-CR. Neither this document nor the information contained herein may be used or disclosed to others without the express written permission of IVAX-CR.

Neoral® capsules/ Eptoral capsules

Study No.: 53/EQ/01/PK
CT I phase**AGREEMENT PAGE****Confidential**

Transmission, duplication or use for publication only with written consent of the pharmaceutical company IVAX-CR, a.s. , Czech Republic.

We hereby declare that the clinical study No.: 53/EQ/01/PK will be carried out in compliance with the clinical study protocol approved by the Independent Ethics Committee and the appropriate state authority, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practice", World Medical Declaration of Helsinki (Edinburgh 2000), in compliance with legal country regulations. All the data of the clinical study are considered to be confidential and the sponsor's property. Their publication is possible only after obtaining the sponsor's consent.

Clinical study was approved by the Ethics Committee:
Date

Addresses and Responsibilities

Coordinator of the study
Professor Marwan Masri
Immunology and Transplantation
Rizk Hospital
P.O. Box 11-3288
Beirut Lebanon
Tel: +9611200800, ext 22094,22331,22330
Fax: +9611792185/+9611200348
Mobile phone:+9613622398
Mobile fax:+9613695201
e-mail: marwan.masri@mysalima.com; marwanmasri@hotmail.com

Signature

Date

Neoral[®] capsules/ Equoral capsulesStudy No.: 53/EQ/01/PK
CT I phase**AGREEMENT PAGE**

Confidential

Transmission, duplication or use for publication only with written consent of the pharmaceutical company IVAX-CR, a.s., Czech Republic.

We hereby declare that the clinical study No.: 53/EQ/01/PK will be carried out in compliance with the clinical study protocol approved by the Independent Ethics Committee and the appropriate state authority, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practice", World Medical Declaration of Helsinki (Edinburgh 2000), in compliance with legal country regulations. All the data of the clinical study are considered to be confidential and the sponsor's property. Their publication is possible only after obtaining the sponsor's consent.

Clinical study was approved by the Ethics Committee: 9/4/2007 Date

Addresses and Responsibilities

Coordinator of the study
 Professor Marwan Masri
 Immunology and Transplantation
 Rizk Hospital
 P.O. Box 11-3288
 Beirut Lebanon
 Tel: +9611200800, ext 22094,22331,22330
 Fax: +96117921854/+9611200348
 Mobile phone: +9613622398
 Mobile fax: +9613695201
 e-mail: marwan.masri@mycelina.com; marwanmasri@hotmail.com


 Signature

20/4/2007
 Date

Clinical Trial Manager, Author of the Protocol and Monitor of SAE
 Bva Kopečná, MD
 Clinical Department of R&D, IVAX-CR a.s., Ostravská 11 J
 747 70 Opava-Komárov, Czech Republic
 Phone: +420/653/642639, Fax: +420/653/642649
 e-mail: bva_kopeчна@ivax-cr.com

 Signature

 Date

Nicornal[®] capsules/ Equeval capsulesStudy No.: 53/EQ/01/PK
CT I phase

AGREEMENT PAGE

Confidential

Transmission, duplication or use for publication only with written consent of the pharmaceutical company IVAX-CR, a.s., Czech Republic.

We hereby declare that the clinical study No.: 53/EQ/01/PK will be carried out in compliance with the clinical study protocol approved by the Independent Ethics Committee and the appropriate state authority, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practice", World Medical Declaration of Helsinki (Edinburgh 2000), in compliance with legal country regulations. All the data of the clinical study are considered to be confidential and the sponsor's property. Their publication is possible only after obtaining the sponsor's consent.

Clinical study was approved by the Ethics Committee:

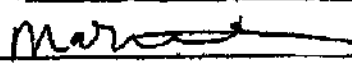
12/4/2002

Date

Addresses and Responsibilities

Coordinator of the study
Professor Marwan Masri
Immunology and Transplantation
Rizk Hospital
P.O. Box 11-3288
Beirut Lebanon
Tel: +9611200800, ext 22094, 22331, 22330
Fax: +9611792185/+9611200348
Mobile phone: +9613622398
Mobile fax: +9613695201
e-mail: marwan.masri@unvsaibn.com, marwanmasri@hotmail.com

Signature



Date

20/4/2002

Clinical Trial Manager, Author of the Protocol and Monitor of SAE
Bva Kopecká, MD
Clinical Department of R&D, IVAX-CR a.s., Ostrava
747 70 Opava-Korndrov, Czech Republic
Phone: +420/653/642639, Fax: +420/653/642649
e-mail: bva_kopecka@ivax-cr.com

Signature

Date

Neorot[®] capsules/ Systamal capsules

Study No.: 53/BQ/01/PK
CT1 phase

AGREEMENT PAGE

Confidential

Transmission, duplication or use for publication only with written consent of the pharmaceutical company IVAX-CR, a.s., Czech Republic.

We hereby declare that the clinical study No.: 53/BQ/01/PK will be carried out in compliance with the clinical study protocol approved by the Independent Ethics Committee and the appropriate state authority, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practice", World Medical Declaration of Helsinki (Edinburgh 2000), in compliance with legal country regulations. All the data of the clinical study are considered to be confidential and the sponsor's property. Their publication is possible only after obtaining the sponsor's consent.

Clinical study was approved by the Ethics Committee: 17/4/2002

Date

Addresses and Responsibilities

Coordinator of the study
Professor Marwan Masri
Immunology and Transplantation
Risk Hospital
P.O. Box 11-3288
Beirut Lebanon
Tel: +9611200800, ext 22094, 22331, 22330
Fax: +9611792185/+9611200348
Mobile phone: +9613622398
Mobile fax: +9613695201
e-mail: marwan.masri@univgalina.com; marwanmasri@hotmail.com

Signature

20/4/2002
Date

Clinical Trial Manager, Author of the Protocol and Monitor of SAZ
Eva Kopecká, MD
Clinical Department of R&D, IVAX-CR a.s., Ostravská 11
747 70 Opava-Komárov, Czech Republic
Phone: +420/653/642639, Fax: +420/653/642649
e-mail: eva_kopecka@ivax-cr.com

Signature

Date

Neoral® capsules/ Equisal capsules

Study No. 53/EQ/01/PK
CT Ipsum**AGREEMENT PAGE****Confidential**

Transmission, duplication or use for publication only with written consent of the pharmaceutical company IVAX-CR, a.s., Czech Republic.

We hereby declare that the clinical study No.: 53/EQ/01/PK will be carried out in compliance with the clinical study protocol approved by the Independent Ethics Committee and the appropriate state authority, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practice", World Medical Declaration of Helsinki (Edinburgh 2000), in compliance with legal country regulations. All the data of the clinical study are considered to be confidential and the sponsor's property. Their publication is possible only after obtaining the sponsor's consent.

Clinical study was approved by the Ethics Committee:

17/4/2002

Date

Addresses and Responsibilities

Coordinator of the study
Professor Marwan Masi
Immunology and Transplantation
Rizk Hospital
P.O. Box 11-3288
Beirut Lebanon
Tel: +9611200800, ext 22094, 22331, 22330
Fax: +96117921854+9611200348
Mobile phone: +9613622398
Mobile fax: +9613695201
e-mail: marwan.masi@univastina.com; marwanmasi@hotmail.com

Signature

20/4/2002
Date

Clinical Trial Manager, Author of the Protocol and Member of SAE
Eva Kopečková, MD
Clinical Department of R&D, IVAX-CR a.s., Ostravská 11
747 70 Opava-Komárov, Czech Republic
Phone: +420/653/642639, Fax: +420/653/642649
e-mail: eva_kopeckova@ivax-cr.com

Signature

Date

Nabent[®] capsules/ Equisal capsulesStudy No.: 53/EQ/01/PK
CT1 phase**AGREEMENT PAGE****Confidential**

Transmission, duplication or use for publication only with written consent of the pharmaceutical company IVAX-CR, a.s., Czech Republic.

We hereby declare that the clinical study No.: 53/EQ/01/PK will be carried out in compliance with the clinical study protocol approved by the Independent Ethics Committee and the appropriate state authority, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practice", World Medical Declaration of Helsinki (Edinburgh 2000), in compliance with legal country regulations. All the data of the clinical study are considered to be confidential and the sponsor's property. Their publication is possible only after obtaining the sponsor's consent.

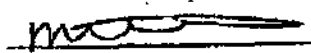
Clinical study was approved by the Ethics Committee:

20/4/2002

Date

Addressees and Responsibilities

Coordinator of the study
Professor Marwan Masi
Immunology and Transplantation
Rizk Hospital
P.O. Box 11-3288
Beirut Lebanon
Tel: +9611200800, ext 22094,22331,22330
Fax: +9611792185/+9611200348
Mobile phone: +9613622398
Mobile fax: +9613695201
e-mail: marwan.masi@nyasabina.com; marwanmasi@hotmail.com


Signature
20/4/2002
Date

Clinical Trial Manager, Author of the Protocol and Monitor of SAE
Eva Kopečná, MD
Clinical Department of R&D, IVAX-CR a.s., Ostrava¹ J
747 70 Opava-Komárov, Czech Republic
Phone: +420/653/642639, Fax: +420/653/642649
e-mail: eva_kopecka@ivax-cr.com

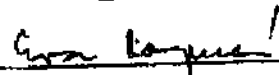
 Signature

 Date

Neoral® capsules/ Efgoral capsules

Study No.: S3/EQ/01/PR
CT III phase

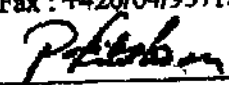
Clinical Trial Manager, Author of the Protocol and Monitor of SAE
Eva Kopečná, MD
Clinical Department of R&D, IVAX-CR a.s., Ostravská 29
747 70 Opava-Komárov, Czech Republic
Phone : +420/653/642639 , Fax : +420/653/642649
e-mail: eva_kopečna@ivax-cr.com



Signature

11.1.2002
Date

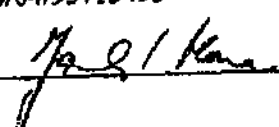
Statistician of the Clinical Part of the Study
RNDr. Dalibor Svoboda
PharmTest s.r.o.
Víta Nejedlého 893, 500 03 Hradec Králové
Phone/Fax : +420/04/95715495



Signature

12/1/2002
Date

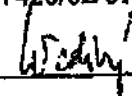
Data Manager of the Clinical Part of the Study
Hana Janská
PharmTest s.r.o.
Víta Nejedlého 893, 500 03 Hradec Králové
Phone/Fax : +420/04/95715495



Signature

11/1/02
Date

Statistician of the Pharmacokinetic Part of the Study
Josef Šedivý, MD, PhD
Vostrovská 33
160 120 00 Praha 6
Phone/Fax: +420/02/61083120



Signature

22/1/2002
Date

COUNTRY INVESTIGATOR'S PROTOCOL AGREEMENT PAGE

I, the undersigned, have read and understood this protocol and hereby agree:

- to assume responsibility for the proper conduct of the study at the trial site
- to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by IVAX-CR
- to comply with all relevant SOPs required for the conduct of this study
- not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Regulatory Authority (where applicable) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- that I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor including, but not limited to the following: the current Investigator's Brochure (IB)/Summary of Product Characteristics (SPC) or equivalent document provided by IVAX-CR and, approved product label, if applicable.
- that I am aware of, and will comply with, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practices" and all applicable country regulatory requirements.
- to ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study related duties and functions as described in the protocol.

Country principal investigator's signature

Date

Name

Title

Name and address of the study site:

Telephone/fax number of the study site:

(The signature and date can not be obtained before the protocol is final. Any other site personnel have to fill in the 'Site personnel log and delegation list' prior enrolment of any subject in to the study.)

Kairo Kidney FAX

PHONE NO. : 5769749

Apr. 09 2002 10:04PM

Neoral[®] capsules/liquoral capsulesStudy No. 53/01/01/02
CT 1phinc

COUNTRY INVESTIGATOR'S PROTOCOL AGREEMENT PAGE

I, the undersigned, have read and understood this protocol and hereby agree:

- to assume responsibility for the proper conduct of the study at the trial site
- to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by IVAX-CR
- to comply with all relevant SOPs required for the conduct of this study
- not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Regulatory Authority (where applicable) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- that I am thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, and any other information provided by the sponsor including, but not limited to the following: the current Investigator's Brochure (IB)/Summary of Product Characteristics (SPC) or equivalent document provided by IVAX-CR and, approved product label, if applicable.
- that I am aware of, and will comply with, ICH 6 (CPM/ICH/135/95) principles of "Good Clinical Practices" and all applicable country regulatory requirements.
- to ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study related duties and functions as described in the protocol.

Country principal investigator's signature

Date

PROF. RAHAB S. FARJOUHCLIC Chairman

Name

Title

Name and address of the study site:

Telephone/fax number of the study site:

(The signature and date can not be obtained before the protocol is final. Any other site personnel have to fill in the 'Site personnel log and delegation list' prior enrollment of any subject in to the study.)

UNIVERSITESI REKTÖRLÜK TEL NO. : 03122123133
PHONE NO. : 561 1 372 259

NIS. 12 2002 14:22
Apr. 12 2002 09:23 AM PC

Noted: regulatory financial regulations

Study No. 521/001/01
CT 1 phase

COUNTRY INVESTIGATOR'S PROTOCOL AGREEMENT PAGE

- I, the undersigned, have read and understood this protocol and hereby agree:
- to assume responsibility for the proper conduct of the study at the trial site
 - to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by IVAX-CR
 - to comply with all relevant SOPs required for the conduct of this study
 - not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Regulatory Authority (where applicable) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)
 - that I am thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, and any other information provided by the sponsor including, but not limited to the following: the current Investigator's Brochure (IB)/Summary of Product Characteristics (SPC) or equivalent document provided by IVAX-CR and, approved product label, if applicable.
 - that I am aware of, and will comply with, ICH 6 (GCP) (ICH/135/95) principles of "Good Clinical Practices" and all applicable country regulatory requirements.
 - to ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study related duties and functions as described in the protocol.

[Signature]
Country principal investigator's signature

[Signature]
Date

Name

Name and address of the study site

Telephone/fax number of the study site

Title

(The signature and date must be obtained before the protocol is final. Any other site personnel known to fill in the 'Site personnel log and delegation list' prior completion of any subject to the study.)

PHONE NO. : 961 1 372 259

Apr. 09 2002 10:58AM PG

Name of Country Principal Investigator

Study No. NCT0010142
C11 place

COUNTRY INVESTIGATOR'S PROTOCOL AGREEMENT PAGE

I, the undersigned, have read and understood this protocol and hereby agree:

- to assume responsibility for the proper conduct of the study at the trial site
- to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by IVAX-CR
- to comply with all relevant SOPs required for the conduct of this study
- not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Regulatory Authority (where applicable) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- that I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor including, but not limited to the following: the current Investigator's Brochure (IB)/Summary of Product Characteristics (SPC) or equivalent document provided by IVAX-CR and, approved product label, if applicable.
- that I am aware of, and will comply with, ICH G (CPMP/MCH/135/95) principles of "Good Clinical Practices" and all applicable country regulatory requirements.
- to ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study related duties and functions as described in the protocol.

Country principal investigator's signature

Date 17/4/2002

Name Dr GABY KAMEL

Name and address of the study site:

Telephone/fax number of the study site:

Title HEAD TRANSPLANTATION
UNIT AT RIZK HOSPITAL

(The signature and date can not be obtained before the protocol is final. Any other site personnel have to fill in the "Site personnel list" prior enrollment of any subject in to the study.)

Vyta Nejedlého 893, 500 03 Hradec Králové
Phone/Fax : +420/04/95715495

Signature

Date

Statistician of the Pharmacokinetic Part of the Study
Josef Dediv, MD, PhD
Vostrovsk33 J
120 00 Praha 6
Phone/Fax: +420/02/61083120

Signature

Date

COUNTRY INVESTIGATOR'S PROTOCOL AGREEMENT PAGE

I, the undersigned, have read and understood this protocol and hereby agree:

- to assume responsibility for the proper conduct of the study at the trial site
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by IVAX-CR
- To comply with all relevant SOPs required for the conduct of this study
- Not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Regulatory Authority (where applicable) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor including, but not limited to the following: the current Investigator's Brochure (IB)/Summary of Product Characteristics (SPC) or equivalent document provided by IVAX-CR and, approved product label, if applicable.
- That I am aware of, and will comply with, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practices" and all applicable country regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study related duties and functions as described in the protocol.

Country principal investigator's signature

Date

Name

Title

Name and address of the study site: BINDH INSTITUTE OF UROLOGY & TRANSPLANTAT

Telephone/fax number of the study site: DOW MEDICAL COLLEGE & CIVIL HOSPITAL KARAI

TEL# 92-21-9215752 / 9215718

FAX# 92-21-9215469 / 9215362

Neoral® capsules/ Eptoral capsules

Study No. 538Q/01/PK
CT I phase**COUNTRY INVESTIGATOR'S PROTOCOL AGREEMENT PAGE**

I, the undersigned, have read and understood this protocol and hereby agree:

- to assume responsibility for the proper conduct of the study at the trial site
- to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by IVAX-CR
- to comply with all relevant SOPs required for the conduct of this study
- not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Regulatory Authority (where applicable) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- that I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor including, but not limited to the following: the current Investigator's Brochure (IB)/Summary of Product Characteristics (SPC) or equivalent document provided by IVAX-CR and, approved product label, if applicable.
- that I am aware of, and will comply with, ICH 6 (CPMP/ICH/135/95) principles of "Good Clinical Practices" and all applicable country regulatory requirements.
- to ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study related duties and functions as described in the protocol.

Country principal investigator's signature

Professor Marwan Meri

Name

Name and address of the study site:

Telephone/fax number of the study site:

20/4/2002

Date

Coordinator

Title

RIZK HOSPITAL P.O Box 11-3288
Beirut - Lebanon

(The signature and date can not be obtained before the protocol is final. Any other site personnel have to fill in the 'Site personnel log and delegation list' prior enrolment of any subject in to the study.)

Neoral® capsules/ Equoral capsules

Study No.:53/BQ/01/PK
CT I phase

**LIST OF CLINICAL LABORATORIES AND OTHER MEDICAL AND/OR
TECHNICAL DEPARTMENT AND/OR INSTITUTIONS INVOLVED IN
THE STUDY**

Name and address

Name of responsible person_____
Title

Telephone/fax number

Name and address

Name of responsible person_____
Title

Telephone/fax number

Name and address

Name of responsible person_____
Title

Telephone/fax number

TABLE OF CONTENTS

TITLE PAGE	1
AGREEMENT PAGE	2
LIST OF CLINICAL LABORATORIES	3
TABLE OF CONTENTS	6
LIST OF APPENDICES	8
LIST OF ABBREVIATION AND DEFINITIONS OF TERMS	9
PROTOCOL SYNOPSIS	10
FLOW CHARTS	14
 1. INTRODUCTION	 15
 2. STUDY OBJECTIVE AND PURPOSE	 17
2.1. Primary objective(s)	17
2.2. Secondary objective(s)	17
2.3. Tertiary objective(s)	17
 3. STUDY DESIGN	 17
3.1. Study endpoint(s)	17
3.1.1. Primary endpoint(s)	17
3.1.2. Secondary endpoint(s)	17
3.1.3. Tertiary endpoint(s)	17
3.2. Overall design	18
3.3. Study centres	18
3.4. Study medication(s)	19
3.5. Storage, disposition and accountability of supplies	21
3.6. Subjects allocation/randomization	21
3.7. Subjects identification list	22
 4. SUBJECT SELECTION CRITERIA	 22
4.1. Planned sample size	22
4.2. Inclusion criteria	22
4.3. Exclusion criteria	23
4.4. Subject withdrawal criteria	24
 5. TREATMENT DURING STUDY	 24
5.1. Treatment assignment	24
5.2. Name of study medication(s), dosage and dosage regimen	25
5.3. Duration of treatment	25
5.4. Concomitant medication and treatment/special dietary requirements	26
5.4.1. Concomitant medication	26
5.4.2. Special dietary requirements	26
5.5. Assessment of compliance	27
 6. ASSESSMENTS / STUDY PROCEDURES	 27
6.1. Assessments of efficacy	28
6.1.1. Pharmacokinetics	28
6.2. Assessments of safety	30
6.2.1. Vital signs	31
6.2.2. Adverse Events	31
6.2.3. Laboratory tests	34
 7. DATA ANALYSIS METHODS/STATISTICS	 36
7.1. Statistical evaluation	36
7.1.1. Primary endpoint(s)	36
7.1.2. Analytical plan	37

Neoral® capsules/ Equoral capsules

Study No. 53/EQ/01/PK
CT Lphos

7.1.3. Secondary endpoint(s).....	37
7.1.4. Tertiary endpoints(s).....	37
7.2. Target sample size	38
7.3. Outliers	38
8. DIRECT ACCESSION TO SOURCE DATA AND DOCUMENTATION.....	38
9. QUALITY CONTROL AND QUALITY ASSURANCE.....	39
9.1. Study monitoring.....	39
9.2. Deviation from protocol.....	39
9.3. Discontinuation of study.....	40
9.4. Quality assurance.....	40
10. REGULATORY AND ETHICAL CONSIDERATIONS.....	40
10.1. Regulatory authority approval.....	40
10.2. Ethical considerations.....	40
10.3. Written informed consent.....	41
10.4. Ethics Committee approval.....	42
11. DATA HANDLING AND RECORDS KEEPING, ARCHIVING OF DATA, AUDIT.....	42
11.1. Data handling.....	42
11.2. Archiving of data.....	42
11.3. Audit.....	42
12. INDEMNIFICATION AND COMPENSATION FOR INJURY.....	43
13. INFORMATION DISCLOSURE AND INVENTIONS.....	43
13.1. Ownership.....	43
13.2. Confidentiality.....	43
13.3. Publication.....	43
14. DATA MANAGEMENT.....	44
14.1. Data collection.....	44
14.2. Source data.....	45
14.3. Data recording.....	45
15. STUDY ADMINISTRATION.....	46
15.1. Sponsor study documentation.....	46
15.2. Study file for the investigator.....	47
15.3. Study and site closure.....	48
16. ANTICIPATED DURATION OF STUDY.....	48
17. RESPONSIBILITIES.....	49
18. REFERENCES.....	50
APPENDICES.....	

Neoral® capsules/ Equoral capsules

Study No.: 53/EC/M/PE
CT I phase

LIST OF APPENDICES

Appendix A	Information for Patients Form/Informed Consent Form
Appendix B	Test Product Information (Equoral capsules, Sandimmun Neoral)
Appendix C	World Medical Association Declaration of Helsinki 1964 (revised 1975, amended 1983, 1989, 1996, and revised 2000, Edinburgh, Scotland)
Appendix D	Blank Case Report Form

Necrol[®] capsules/ Equoral capsulesStudy No.: S3/EQ/01/PK
CT 1 phase**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

AE	Adverse event
ALAT	Alanine aminotransferase
ANOVA	Analysis of variance
ASAT	Aspartate aminotransferase
AUC	Area under the curve
AUMC	Area under the 1st moment concentration-time curve
BP	Blood pressure
Bpm	Beats per minute
BTL	Blood trough level
BUN	Blood urea nitrogen (Urea)
C ₀ , C ₁ , C ₂	Concentration before (1 hr after, 2 hrs after) drug administration
C _{max}	Maximum concentration
C _{min}	Minimum concentration
CyA	Cyclosporine A
CRF	Case report form
F _{rel}	Relative bioavailability
FW	Blood Sedimentation Rate
GCP	Good clinical practice
GMT	Glutamyl transpeptidase
H, hr, hrs	Hour(s)
Hb	Hemoglobin
HCT (PCV)	Haematocrit
IC	Informed consent
ICH-GCP	International conference on Harmonization – Good Clinical Practice
λ_z	Terminal elimination rate constant
mg	Milligram
min(s)	Minute(s)
mL	Millilitre
PK	Pharmacokinetic
PLT	Platelets
PTF	Peak-trough-fluctuation
RBC	Red blood cell
SAE	Serious adverse event
SEM	Standard error of the mean
SGC	Soft gelatin capsule
SOP	Standard operating procedure
ss	steady state
t _{1/2el}	Half-life of drug elimination
T _{max}	Time to maximum concentration
Tx	Transplantation
U	Urinalysis
WBC	White blood cell count

Neoral® capsules/ Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase

PROTOCOL SYNOPSIS

Title:	A Pharmacokinetic Conversion Study of EQUORAL (IVAX-CR) and NEORAL® in Stable Adult Renal Transplant Recipients
Study number:	53/EQ/01/PK
IVAX project number:	01000105
Investigational drug:	Equoral capsules 25 mg, 50 mg, 100 mg IVAX-CR a.s., Opava-Komárov The Czech Republic
Reference drug:	Neoral® capsules 25 mg, 50 mg, 100 mg, Novartis
Clinical Phase:	Phase I.
Sponsor's responsibility for the project:	Assoc.Prof.Vojtěch Kamarád MD, ScD Clinical department R&D, IVAX-CR a.s Ostravská 29, 747 05 Opava-Komárov
Principal Investigator and coordinator:	Professor Marwan Masri Immunology and Transplantation Rizk Hospital, P.O. Box 11-3288, Beirut Lebanon
Study centers:	Professor Gaby Kamel Chairman Transplant Department Rizk Hospital P.O. Box 11-3288 Beirut Lebanon Professor Rasahd Barsoum Chairman of internal Medicine & Chief of Nephrology University of Cairo Secretary-General of the international society of Nephrology Cairo Kidney Center Bab-Bi-Louk 11513 Cairo Egypt Professor Mehmet Haberal Rector, Baskent University Director Transplantation Unit Cadde No: 77 Kat: 4 Bahcalievler Ankara 06490 Turkey Professor Ahad J. Ghods, M.D., F.A.C.P. Hashemi Nejad Kidney Hospital Vanak Square 19396 Tehran - Iran Professor Syed Adibul Rizvi Director Sindh Institute of Urology and Transplantation (SIUT) Dow medical collage and Civil Hospital Karachi 74400, Pakistan
Analytical center:	Immunoanalytical Laboratory in each clinical center with validated TDx Abbott monoclonal specific antibody methodology
Primary objective:	The primary objective of the study is to compare pharmacokinetics of the new generic cyclosporine formulation - Equoral capsules after the switch from original formulation Neoral® capsules in stable adult renal transplant recipients
Secondary objective:	The secondary objective of the study is to evaluate C1, C2, BTL and changes in dosage of CyA

Neoral® capsules/ Equoral capsules

Study No.: 53/BQ/01/PK
CT Phase

Tertiary objective:	The tertiary objective of the study is to evaluate the safety of the switch from Sandimmun® Neoral capsules to Equoral capsules
Primary endpoint:	Steady-state extent and rate parameters correlated for the dose (AUC _τ , Peak-trough-fluctuation, C _{min-ss} , C _{max-ss}) and their variabilities before and after the switch 1:1 (milligram: milligram) from Neoral capsules to Equoral capsules
Secondary endpoints:	C ₁ , C ₂ , BTL, oral daily dose of cyclosporine, number of dose adjustments
Tertiary endpoints:	Vital signs, incidence of adverse events, changes in blood pressure, laboratory variables
Number of subjects:	100
Study design:	Multi-center, multinational, open label, conversion clinical trial
Critical inclusion criteria:	1. Either sex 2. Age: 18-70 years 3. First renal transplant (cadaveric or living donor) 4. No rejection episode in the past 6 months 5. Clinically stable for at least 6 months post transplantation with acceptable safety/tolerance to Sandimmun® Neoral capsules 6. Three last whole blood trough cyclosporine levels in the range of 70-200 ng/ml (RIA specific) 7. Stable serum creatinine in the past 3 months with no trend to increase 8. No hepatic dysfunction in the past 6 months (increase of aminotransferase <100 % above the limit) 9. No history of alcohol or drug abuse or signs of alcohol-induced organ damage 10. No clinical symptoms of CMV infection in the past 6 months 11. No history or evidence of malignancy or any significant infection 12. Blood pressure in normotensive range with or without antihypertensive medication 13. Maintained on cyclosporine in double or triple combination with prednisone, azathioprine, mycophenolate mofetil 14. Doses of cyclosporine ≤ 8 mg/kg/day. The dose has to be stable over the previous 14 days prior to entry 15. Doses of concomitant medication stable 14 days prior to study entry 16. Subject's ability to communicate well with the investigator 17. Written informed consent is to be obtained 18. Subject has not participated in another clinical trial within 28 days preceding this study
Critical exclusion criteria:	1. Significant history of hypersensitivity to cyclosporine or any related products 2. Significant history of hypersensitivity to castor oil, olive oil or corn oil 3. Pregnancy or lactating females 4. Premenopausal woman of childbearing potential not using safe contraception 5. >1 renal transplant or grafts of other organs (e.g., pancreas) 6. Use of routine immunosuppressive therapy other than azathioprine, mycophenolate mofetil or prednisone 7. Uncontrolled blood pressure (resistant to antihypertensive therapy and despite reduction of cyclosporine dose) 8. History of chronic alcoholism, drug or narcotic abuse 9. History of myocardial infarction within 6 months of enrollment or uncontrolled cardiac arrhythmia

Neoral® capsules/ Equoral capsules

Study No.:53/BQ/01/PK
CT I phase

	10. Clinically relevant disease (including nervous system) or other abnormal condition which may compromise function of gastrointestinal tract, kidney or liver or which might influence cyclosporine pharmacokinetics. 11. Exposition to any drug interfering with cyclosporine pharmacokinetics within 14 days prior to study entry 12. Exposition to any potentially nephrotoxic drug during 14 days prior to study entry 13. Subjects with significant medical problems or unstable disease states
Procedures	Stable renal transplant recipients ≥ 6 months post transplantation on Neoral® capsules BID therapy will be screened in the pre-study period on the basis of inclusion and exclusion criteria. On the day -7 cyclosporine blood trough level will be determined, and samples for hematology, biochemistry and urine chemistry will be collected. The subjects who fulfil the inclusion and exclusion criteria will be enrolled in the study on the day 0 when the first sparse sampling PK (R) will be performed. On the day 14 the 12-hour PK (R) will be performed. On the day 15 in the morning the patients will be switched from Neoral® capsules BID to Equoral capsules BID at an equivalent dosage (milligrams: milligrams). The second sparse sampling PK (T) will be performed on the day 21 and the 12-hour PK (T) will be performed on the day 28. On the day 29 in the morning the patients will be switched from Equoral capsules BID to Neoral® capsules BID at an equivalent dosage (mg:mg). Additional BTL will be measured on days 18 and 35. In the afternoon before each 12-hour PK the subjects will be admitted and hospitalized in the clinical unit until discharged after the 12-hour pharmacokinetic parts. During each pharmacokinetic part of study 12 blood samples will be taken. The doses of Equoral or Neoral will be individualized to maintain whole blood trough levels of cyclosporine between 70-200 ng/mL (TDx, Abbot). The samples for hematology, biochemistry and urinalysis will be collected also on the day 21. Safety parameters will be monitored at each visit (vital signs, physical examinations, number of routine laboratory parameters, incidence of adverse events).
Twelve-hour pharmacokinetic profiles	On the days 14(R), 28(T)
Sampling time:	Pre-dose, 30 min; 1h; 1h 30 min; 2h; 3h; 4h; 5h; 6h; 8h; 10h and 12hours In all 12 samples will be collected in each period.
Sparse sampling PK	On the days 0(R), 21(T)
Additional BTL	At screening, and on the days 18, 35
Blood loss	Approximately 24 mL of PK blood samples (2x12 samples of 1 mL each) Sparse sampling (2x3 samples of 1 mL each) 3 mL of blood sample for BTL 10 mL of blood withdrawn for screening and 10 mL of blood for safety assessments on the day 21
Main pharmacokinetic parameters	Primary: AUC, C_{max} , Peak-Trough-Fluctuation (PTF), C_{min} , C_{min} , T_{max}
Main parameters of safety	Physical examination, vital signs, adverse events, body weight, laboratory examinations

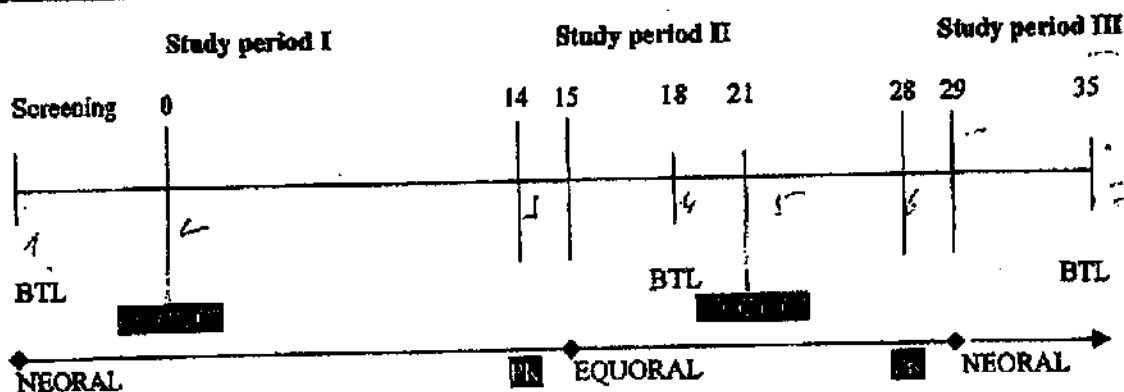
Statistical analysis of pharmacokinetics	Descriptive analysis for the pharmacokinetic parameters including mean, standard deviation, geometric mean, and 95 % confidence intervals. After the log-data transformation, parametric (and non-parametric) statistical analysis with ANOVA model with subject, treatment-phase, and study center as factors will be performed. Additive model and non-parametric statistical analysis will be used for analysis of T_{max} . The test/reference ratio of the parameters incl. their 90% confidence intervals will be accepted using limit of 0.80, 1.25 (AUC_t , PTF) and 0.70, 1.43 (C_{min}), resp.
Statistical analysis of clinical part of the study	Demographic characteristics at baseline, number of dose adjustments, daily doses of cyclosporine, incidence of adverse events will be analyzed using appropriate non-parametric tests. C0, C1, and C2 will be analyzed. Newly occurring adverse events will be categorized and listed by treatment group. Laboratory variables will be calculated by non-parametric statistics
Visits	Screening -7 day, 0 day, 13 day, 21 day, 18 day, 27 day, 35 day
Hospitalization	Days 13 to 15, 27 to 29
Ethics committees	IBC of each study center
Planned study duration:	Screening: -1 week Study period I: 2 weeks Study period II: 2 weeks Study period III: 1 week
Start of the study:	April 2002
End of patient's recruitment	May 2002
Last patient completed	June 2002

Neoral® capsules/ Equoral capsules

Study No. 53/BQ/01/PK
CT I phase

STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

	Screening	Study period I			Study period II			Study period III		
Visit	1	2	3			4	5	6		
Day	-7	0	13	14	15	18	21	27	28	29
General medical history	X									
Demographic data	X									
Physical examination, Vital signs	X	X	X			X	X	X		
Informed consent	X									
Subject selection criteria	X									
Hematology Biochemistry Urine chemistry	X						X			
CyA blood trough level	X					X				X
Sparse samplings PK		X					X			
Pharmacokinetics			X					X		
Drug dispensing			At the discharge from hospital							
Adverse events assessment		X	X			X	X	X		
Concomitant medication		X	X			X	X	X		



1. INTRODUCTION

Cyclosporine is a cyclic polypeptide consisting of 11 amino acids. It has unique immunosuppressive properties and has been extensively used in transplant recipients in the prevention of allograft rejection or the treatment of graft-versus-host disease. Oral doses of cyclosporine vary with indication (depends i.a. on the transplanted organ, time after the transplantation, combination with other immunosuppressants), and range from as low of 3 mg/kg/day as a maintenance dose to as high of 15 mg/kg in a single dose before solid organ transplantation.

Cyclosporine is used alone or in combination with other immunosuppressive drugs to prevent or treat organ rejection following kidney, liver, and heart transplant. Cyclosporine has been shown to be highly effective in a variety of other diseases with an autoimmune component (rheumatoid arthritis, uveitis, nephrotic syndrome, psoriasis vulgaris, atopic dermatitis).¹ It has also been utilized alone or in combination with other medications in the treatment of aplastic anemia, ulcerative colitis, dermatomyositis, systemic lupus erythematosus, Alport's syndrome, amyotrophic lateral sclerosis, biliary cirrhosis and the other less frequent diseases.¹

Cyclosporine, ATC code L04AA01, is a lipophilic cyclic polypeptide, which produces calcium-dependent, specific and reversible inhibition of immunocompetent lymphocytes in the G₀- and G₁-phase of the cell cycle. Within the cell, the cyclosporines bind to immunophilin (cyclophilin), forming complexes which inhibit serine/threonine phosphatase calcineurin. The nuclear translocation of the cytoplasmic subunit of the T-lymphocytes is preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine inhibits cytokine production and release including interleukin-2 or T-cell growth factor. This reduces the cell-mediated immunity. No effects on phagocytic function or tumor cells have been detected. Cyclosporine does not cause bone marrow suppression in animal models or in man. Small changes in the cyclosporine structure influence the efficacy of the drug. Besides cyclosporine, low immunomodulating activity is obtained with only four other cyclosporine metabolites.³

Several therapeutic features, in addition to the marked pharmacokinetic variability, define CyA as a critical drug. Cyclosporine:

- displays narrow therapeutic range between ineffective and toxic drug concentrations, with the possibility of life-threatening consequences in cases of overdosing and underdosing

Neoral® capsules/ Equoral capsules

Study No.: 13/BQ01/FK
CT I phase

- shows high interindividual and intraindividual variability of pharmacokinetic parameters
- displays limited and erratic gastrointestinal absorption, which is formulation dependent
- requires blood level monitoring
- shows only modest utility of body weight indexing to determine dosing

Moreover, there are frequent pharmacokinetic interactions between cyclosporine and other co-administered drugs competing for its metabolism by the intestinal and hepatic cytochrome P450 systems (CYP3A4). Besides cyclosporine, there are well-known substrates of CYP3A4 system, i.e. methylprednisolone, erythromycin, nifedipine, quinidine, lidocaine, statins, warfarin, terfenadine, astemizole, cisapride, carbamazepine, midazolam, and triazolam. CYP3A4-inducers (phenobarbital, dexamethasone, rifampin) or CYP3A4-inhibitors (ketoconazole, itraconazole, erythromycin, diltiazem, verapamil) are often administered to transplant patients, too.

The physical characteristics of the different formulations influence the rate and extent of cyclosporine absorption and their interindividual variability.

Equoral capsules - the new IVAX-CR galenic formulation of cyclosporine is the generic formulation of cyclosporine to Sandimmun® Neoral capsules. Bioequivalence of the both formulations has been approved in healthy volunteers under fed and fasting conditions.^{4,5} The new formulation has resulted in increased bioavailability and less variability in cyclosporine pharmacokinetics and shows a significantly improved correlation between both trough level (C_{min}) and dose.

Although cyclosporine belongs to narrow therapeutic index drug and bearing in the mind the comparison of parameter's intrasubject variability appears to be a good indicator of switchability^{8,15}, the comparative, non-randomized, steady-state pharmacokinetic conversion study with fixed non-replicate study design (R - T) in stable adult renal allograft recipients is to be performed. Nevertheless, the aim of the study is to assess safety and feasibility of 1:1 conversion and to establish an appropriate procedure to switch subjects safely from Sandimmun® Neoral capsules to Equoral capsules. The study does not fulfil the ordinary bioequivalence criteria.

2. STUDY OBJECTIVE AND PURPOSE

2.1 PRIMARY OBJECTIVE (S)

The primary objective of the study is to compare pharmacokinetics of the new generic cyclosporine formulation - Equoral capsules after the switch from original formulation Neoral® capsules in stable adult renal transplant recipients

2.2 SECONDARY OBJECTIVE (S)

The secondary objective of the study is to evaluate C₁, C₂, BTL and changes in dosage of CyA

2.3 TERTIARY OBJECTIVE (S)

The tertiary objective of the study is to evaluate the safety of the switch from Sandimmun® Neoral capsules to Equoral capsules in stable adult renal transplant recipients.

3. STUDY DESIGN

3.1. STUDY ENDPOINT (S)

3.1.1 Primary endpoint(s)

As the primary endpoints the steady-state extent and rate pharmacokinetic parameters correlated for the dose (AUC_T, Peak-trough-fluctuation, C_{min-ss}, C_{max-ss}) and their variabilities will be assessed before and after the switch 1:1 (milligram: milligram) from Neoral capsules to Equoral capsules.

3.1.2 Secondary endpoint(s)

As the secondary endpoints:

- C₀, C₁, C₂
- Oral daily dose of cyclosporine and number of dose adjustments

3.1.3. Tertiary endpoint(s)

As the tertiary endpoints the following parameters will be assessed:

- physical examinations
- vital signs
- incidence of adverse events
- changes in blood pressure
- laboratory variables

Neoral® capsules/ Equoral capsules

Study No.: 53BEQ/G1/PK
CT I phase

3.2. OVERAL DESIGN

The study will be conducted as a multi-center, multinational, open label, pharmacokinetic, conversion clinical study.

3.3. STUDY CENTRES

The study will be performed in the following centers:

Professor Marwan Masri
Immunology and Transplantation
Rizk Hospital
P.O. Box 11-3288, Beirut Lebanon

Professor Gaby Kamel
Chairman Transplant Department
Rizk Hospital
P.O. Box 11-3288 Beirut Lebanon

Professor Rasahd Barsoum
Chairman of internal Medicine & Chief of Nephrology
University of Cairo
Secretary-General of the international society of Nephrology
Cairo Kidney Center
Bab-El-Louk 11513 Cairo Egypt

Professor Mehmet Haberal
Rector, Baskent University
Director Transplantation Unit
Cadde No: 77 Kat: 4 Bahcelievler Ankara 06490 Turkey

Professor Syed Adibul Rizvi
Director
Sindh Institute of Urology and Transplantation (SIUT)
Dow medical collage and Civil Hospital
Karachi 74400, Pakistan

Professor Ahad J. Ghods, M.D., F.A.C.P.
Hashemi Nejad Kidney Hospital
Vanak Square
19396 Tehran - Iran

Neoral® capsules/ Equoral capsules

Study No.:53/EQ/01/PK
CT I phase**3.4. STUDY MEDICATIONS**

The sponsor shall supply adequate investigational product supplies, for dose administration and samples retention purposes, of the test drug and the reference drug. The investigational drugs will be supplies in sealed packages or strips labelled with product name, strengths, study number, batch number, expiration date, storage conditions and manufacturer. The principal investigator of each clinical site will receive the drug products with certificates of analysis.

♦ TEST FORMULATION

Name of products, active substance and its amount:

Equoral capsules (ciclosporinum)

Capsules are available at 25, 50, and 100 mg strengths.

50 capsules per packaging.

Storage

Store at a temperature below +25°C. Capsules should be kept in the blisters before use. Capsules should not be stored in a cold place and should be protected from frost.

Labelling

For clinical trials!	Study No.:53/EQ/01/PK
Subject code ____/____/____	
Equoral 25 mg, capsules	
Ciclosporinum	
For internal use. Do not store in cold, protect from frost.	
Store at a temperature below +25° C.	
Keep out of the reach of children! Keep the capsules in the immediate blister pack until its use.	
Exp. Date:	
Batch No.:	
IVAX-CR a.s., Ostravská 29	
747 70 Olomouc-Komárov, Czech Republic	

For clinical trials! Study No.:53/EQ/01/PK

Subject code _ _ _ / _ _ / _ _ _

Equoral 50 mg, capsules

Ciclosporinum

For internal use. Do not store in cold, protect from frost.

Store at a temperature below +25° C.

Keep out of the reach of children! Keep the capsules in the immediate blister pack until its use.

Exp. Date:

Batch No.:

IVAX-CR a.s., Ostravská 29

747 70 Olava-Komárov, Czech Republic

For clinical trials! Study No.:53/EQ/01/PK

Subject code _ _ _ / _ _ / _ _ _

Equoral 100 mg, capsules

Ciclosporinum

For internal use. Do not store in cold, protect from frost.

Store at a temperature below +25° C.

Keep out of the reach of children! Keep the capsules in the immediate blister pack until its use.

Exp. Date:

Batch No.:

IVAX-CR a.s., Ostravská 29

747 70 Olava-Komárov, Czech Republic

♦ REFERENCE FORMULATION

Name of product, active substance and its amount:

Sandimmun[®] Neoral capsules (ciclosporinum)

Capsules are available at 25, 50, and 100 mg strengths.

Storage

Store at temperature below +25°C. Capsules should be kept in the blisters before use. Capsules should be kept out of frost and cold.

Labelling

For clinical trials! Study No.:53/EQ/01/PK

Subject code ____/____/____

Sandimmun Neoral 25 mg, capsules

Ciclosporinum

For internal use. Do not store in cold, protect from frost.

Store at a temperature below +25° C.

Keep out of the reach of children! Keep the capsules in the immediate blister pack until its use.

Exp. Date:

Batch No.:

NOVARTIS PHARMA AG, BASEL
Switzerland

For clinical trials! Study No.:53/EQ/01/PK

Subject code ____/____/____

Sandimmun Neoral 50 mg, capsules

Ciclosporinum

For internal use. Do not store in cold, protect from frost.

Store at a temperature below +25° C.

Keep out of the reach of children! Keep the capsules in the immediate blister pack until its use.

Exp. Date:

Batch No.:

NOVARTIS PHARMA AG, BASEL
Switzerland

For clinical trials! Study No.:53/EQ/01/PK

Subject code ____/____/____

Sandimmun Neoral 100 mg, capsules

Ciclosporinum

For internal use. Do not store in cold, protect from frost.

Store at a temperature below +25° C.

Keep out of the reach of children! Keep the capsules in the immediate blister pack until its use.

Exp. Date:

Batch No.:

NOVARTIS PHARMA AG, BASEL
Switzerland

3.5. STORAGE, DISPOSITION AND ACCOUNTABILITY OF SUPPLIES

The Clinical Study Material for this study must be used in accordance with the Protocol. The principal investigator shall keep and maintain complete and accurate records of investigational material. Drug supplies are to be stored in a locked cabinet in the Principal Investigator's office. Records showing the receipt and disposition of all materials shall include a master record listing the date drug shipment was received, the quantities received, and a dispensing record which includes

each quantity dispensed, identification of the person to whom dispensed, the date of dispensing or accidentally destroyed, and the identification of the dispenser. All non-used investigational medication will be returned to the Sponsor and a certificate "Drug return form" will be provided to the sponsor.

3.6. SUBJECTS ALLOCATION/RANDOMIZATION

100 subjects in 5 clinical centers (each center maximum 20 subjects) who will fulfil inclusion and exclusion criteria will be enrolled into the study. Each patient will be designated by the following code:

XYZ	/	digit digit	/	digit digit
↓		↓		↓
Subject's initials		Order of subject's		Center's number
(First name, second name, family name)		enrollment to the study		

(For example ABC/01/01)

3.7. SUBJECT IDENTIFICATION LIST

According to the ICH-GCP guidelines the investigator has to maintain a subject identification list which ensures a distinctive identification of the subjects by their name to screening number, initials, complete name, date of birth, and date of signing of Informed consent. The investigator has to archive this identification list according to section 4.9.5. of ICH-GCP guidelines and in compliance with local legal regulations and legislative.

4. SUBJECT SELECTION CRITERIA

4.1. PLANNED SAMPLE SIZE

100 stable adult renal transplant recipients will be enrolled. Subsequent dropouts will not be replaced.

4.2. INCLUSION CRITERIA

1. Either sex
2. Age: 18-70 years
3. First renal transplant (cadaveric or living donor)
4. No rejection episode in the past 6 months

5. Clinically stable for at least 6 months post transplantation with acceptable safety/tolerance to Sandimmun Neoral capsules
6. Three last whole blood cyclosporine trough levels in the range of 70- 200 ng/ml (RIA specific)
7. Stable serum creatinine in the past 3 months with no trend to increase
8. No hepatic dysfunction in the past 6 months (increase of aminotransferase <100 % above the limit)
9. No history of alcohol or drug abuse or signs of alcohol-induced organ damage
10. No clinical symptoms of CMV infection in the past 6 months
11. No history or evidence of malignancy or any significant infection
12. Blood pressure in normotensive range with or without antihypertensive medication
13. Maintained on cyclosporine in double or triple combination with prednisone, azathioprine, mycophenolate mofetil
14. Doses of cyclosporine < 8 mg/kg/day. The dose has to be stable over the previous 14 days prior to entry
15. Doses of concomitant medication stable 14 days prior to study entry
16. Subject's ability to communicate well with the investigator
17. Written informed consent is to be obtained
18. Subject has not participated in another clinical trial within 28 days preceding this study

4.3. EXCLUSION CRITERIA

1. Significant history of hypersensitivity to cyclosporine or any related products
2. Significant history of hypersensitivity to castor oil, olive oil or corn oil
3. Pregnancy or lactating females
4. Premenopausal woman of childbearing potential not using safe contraception
5. >1 renal transplant or grafts of other organs (e.g., pancreas)
6. Use of routine immunosuppressive therapy other than azathioprine, mycophenolate mofetil or prednisone
7. Uncontrolled blood pressure (resistant to antihypertensive therapy and despite reduction of cyclosporine dose)
8. History of chronic alcoholism, drug or narcotic abuse

9. History of myocardial infarction within 6 months of enrollment or uncontrolled cardiac arrhythmia
10. Clinically relevant disease (including nervous system) or other abnormal condition which may compromise function of gastrointestinal tract, kidney or liver or which might influence cyclosporine pharmacokinetics.
11. Exposition to any drug interfering with cyclosporine pharmacokinetics 14 days prior to study entry
12. Exposition to any potentially nephrotoxic drug during two weeks prior to study entry
13. Subjects with significant medical problems or unstable disease states

4.4. SUBJECT WITHDRAWAL CRITERIA

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The principal investigator has also the right to withdraw subjects from the study in case of serious adverse events necessity to take any of excluded medication, protocol violations, withdrawal of consent, failure to return for schedule visit or other reason. The subjects may also be withdrawn if necessary to protect their health and the integrity of the study. In case of questionable situation the Clinical Trial Monitor or the Medical Contact must be consulted. Continued participation of any patient who violates the protocol will be decided by the Sponsor's Medical Contact. Patients who are not evaluable due to protocol violations that were within the control of the investigator will not be considered as completed subjects. Subjects who do not complete the study will not be replaced. Subjects who withdraw due to adverse events will be classified as „completed“ and will not be replaced. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the subject is withdrawing from the study. Each case of subject's withdrawal has to be recorded in the CRF.

5. TREATMENT DURING STUDY

5.1. TREATMENT ASSIGNMENT

Subjects who meet the entry criteria will be allocated in each center consecutive order, starting with the number 1. Study medication will be provided by the sponsor to the CRO.

The CRO will supply clinical site according to:

Local Drug Laws

ICH-GCP guidelines

Relevant SOPs

5.2. STUDY MEDICATION

♦ TEST FORMULATION

IVAX-CR, Opava - Komárov, The Czech Republic:

EQUORAL CAPSULES (ciclosporinum)

To be administered with any non-alcoholic beverages except of grapefruit juice.

On the day 15 in the morning the subjects will be switched from Sandimmun® Neoral capsules to Equoral capsules at an equivalent dosage (milligrams: milligrams). Individual dosage will be adjust according to whole blood cyclosporine trough levels to maintain them within therapeutic range 70-200 ng/mL. The administration of Equoral will end on the day 28 with the evening dose.

♦ REFERENCE FORMULATION

NOVARTIS, Switzerland:

SANDIMMUN® NEORAL SGC (ciclosporinum)

To be administered with any non-alcoholic beverages except of grapefruit juice.

Subjects on stable Sandimmun® Neoral capsules therapy will be switched to Equoral capsules at an equivalent dosage (milligrams: milligrams) on the day 15 in the morning and then re-switched at an equivalent dosage (milligrams: milligrams) on the day 29 in the morning. Individual dosage will be adjust according to whole blood cyclosporine trough levels to maintain them within therapeutic range 70-200 ng/mL.

Rejection therapy

Acute rejection will be treated by 500 mg of methylprednisolone iv for 3 days. In cases of steroid-resistant acute rejection the investigator can continue with methylprednisolone or administer a rabbit antihuman thymocytes globulin preparation or other approved monoclonal antibodies.

5.3. DURATION OF TREATMENT

Sandimmun® Neoral capsules: from the day 1 to the day 14, and from the day 29 to the day 35.

Equoral capsules: from the day 15 to the day 28.

5.4.CONCOMITANT MEDICATION AND TREATMENT/ SPECIAL DIETARY REQUIREMENTS

Cyclosporine displays marked inter-individual pharmacokinetic variability, due to its erratic and formulation dependent absorption, and to its metabolism by the intestinal and hepatic cytochrome P 450 systems (CYP3A4). There are frequent pharmacokinetic interactions between cyclosporine and competing substrate for CYP3A4 (among them methyprednisolone, erythromycin, nifedipine, lidocain, statins, warfarin, terfenadine, astemizole, cisapride, carbamazepine, midazolam, triazolam), CYP3A4-inducers (phenopharbitol, dexamethasone, rifampycine), or CYP 3A4-inhibitors (ketokonazole, itraconazole, erythromycin, diltiazem, verapamil).

5.4.1. Concomitant medication

If, for medical reasons any new medication is administered during the study, the investigator should record all pertinent information. Subjects who require medication for other than concomitant disease (e.g., antihypertensives), must be on the same daily requirements for at least 14 days. When agents are administered for medical reasons that are know to interfere with the activity of cytochrome P-450, or bile metabolism or gastric emptying, additional trough blood cyclosporine levels are to be determined during these periods of concomitant therapy. If necessary, adjustments of cyclosporine doses can be made to keep within the specified target blood levels. All dose adjustments are to be made only by the Principal Investigator or his/her designee. All concomitant medication must be recorded in the case report forms with drug generic name, the explicit indication(s) for the drug, international disease code, daily dose and dosing frequency, dates (start/stop) and time of administration.

5.4.2. Special dietary requirements

During housing a standardized menu will be served for all the PK periods. Information on the amount of meal consumed and the time taken for consuming will be recorded in the appropriate clinical raw data sheets. The actual time of meal distributions will also be recorded.

The consumption of alcohol or xanthine-containing beverages and food (chocolates, tea, coffee or cola drinks) will be prohibited for 24 hours before dosing and throughout the period of sample collection. The consumption of grapefruits, grapefruit juice or grapefruit-containing beverages and food will be prohibited for 3 days before dosing and throughout the duration of the pharmacokinetic study. Cigarettes and tobacco products will be prohibited throughout their stay at the clinical facility. On the days of PK study the subjects will have fasted overnight for 10 hours prior to drug intake.

5.5. ASSESSMENT OF COMPLIANCE

Subjects will be instructed to follow the instruction of the investigator and/or study nurse. Compliance will be assessed by a count of returned study medication capsules and packaging materials at the scheduled clinic visits and on the basis of comparison of the relationship between trough levels and dosage. Compliance for dosing during PK part of the study will be assessed by examination of the oral cavity of the subjects by the trained study personnel after dose administration in each period.

6. ASSESSMENTS/STUDY PROCEDURES

Stable renal transplant recipients ≥ 6 months post transplantation on Neoral® capsules BID therapy will be screened in the pre-study period on the basis of inclusion and exclusion criteria. On the day -7 cyclosporine blood trough level will be determined, and samples for hematology, biochemistry and urine chemistry will be collected. The subjects who fulfil the inclusion and exclusion criteria will be enrolled in the study on the day 0 when the first sparse sampling PK (R) will be performed. On the day 14 the 12-hour PK (R) will be performed. On the day 15 in the morning the patients will be switched from Neoral® capsules BID to Equoral capsules BID at an equivalent dosage (milligrams: milligrams). The second sparse sampling PK (T) will be performed on the day 21 and the 12-hour PK (T) will be performed on the day 28. On the day 29 in the morning the patients will be switched from Equoral capsules BID to Neoral® capsules BID at an equivalent dosage (mg:mg). Additional BTL will be measured on days 18 and 35.

In the afternoon before each 12-hour PK the subjects will be admitted and hospitalized in the clinical unit until discharged after the 12-hour pharmacokinetic parts. During each pharmacokinetic part of study 12 blood samples will be taken. The doses of Equoral or Neoral will be individualized to maintain whole blood trough levels of cyclosporine between 70-200 ng/mL (TDx Abbot). The samples for hematology, biochemistry and urinalysis will be collected also on the day 21. Safety parameters will be monitored at each visit (vital signs, physical examinations, number of routine laboratory parameters, incidence of adverse events). During the study the efficacy and safety parameters will be monitored according to the flow chart. All data collected on each subject enrolled in the study must be noted in the individual CRF.

6.1. ASSESSMENT OF EFFICACY**6.1.1. Pharmacokinetics****6.1.1.1. Hospitalization**

The subjects will be admitted and housed in the clinical facility on the day prior to each 12-hour PK part and will stay hospitalized until discharged 12 hours after drug administration. In case of any adverse event, necessary action will be taken till the event subsides.

6.1.1.2. Administration

The drug will be administered between 7 and 8 a.m in the clinical unit to the subjects while in sitting posture. The administration will always be done under medical supervision. They subjects will be instructed to engage in normal activity for the first 4 hours after drug administration, avoiding both vigorous exertion and complete rest. Capsules will be swallowed whole and flushed down with 200 ml of water. The same production lot of water will be used in each phase of the study.

6.1.1.3. Diet

Standardized menu in each center will be served for both 12-hour PK periods.

6.1.1.4. Flow chart of pharmacokinetic part
Assessments in detail

Applicable to Treatment	Time relative to Drug intake (oral dose)	Approx. Clock Time (h. min.)	Adverse Events	Sampling for 12-hour Pharmacokinetic Evaluation	Vital signs	Posture Upright	Hospitalized
N or E	0	08.00	DRUG ADMINISTRATION		X		
		08.10	STANDARDIZED BREAKFAST				
	30 min		X	X			
	1 h		X	X			
	1 h 30 min		X	X			
	2 h		X	X	X		
	3 h		X	X		↓	
	4 h				X		
		12.30	STANDARDIZED LUNCH				
	5 h		X	X			
	6 h		X	X	X		
	8 h		X	X			
		17.30	STANDARDIZED DINNER		X		
	10 h		X	X			
	12 h		X	X	X		↓

Treatment N: Sandimmun® Neoral capsules (Novartis, Switzerland)
Treatment E: Equoral capsules (IVAX-CR a.s.)

Due to the sensitivity of cyclosporine to ultraviolet light, samples will be collected and processed under conditions which will minimize their UV exposure. Whole blood samples (each sample approx. 1 mL) will be collected at the times specified under STUDY DESIGN. The clock time of all blood draws will be recorded and reported for each subject. Any deviation from the sampling schedule will be recorded in the subject's sampling time sheet. Sampling time sheets for all subjects will be included in the CRF. The total volume of blood withdrawn over 12-hours of pharmacokinetic analysis will not exceed 14 mL. The blood samples will be collected in appropriately labeled Tapval® EDTA-containing tubes. The tubes will be labeled with the study identification number and a code that corresponds to subject identifier and sampling time and period. Immediately after collection, the filled blood collection tubes will be inverted gently and frozen at -20° C, and stored in a refrigerator with a regular temperature record.

6.1.1.5. Cyclosporine blood level monitoring and labeling of the tubes

Each tube with CyA blood level determination will be labeled separately in each clinical site according to the following schedule:

Determination of BTL

The whole blood will be taken 5 minutes prior to dosing.

DETERMINATION OF BLOOD TROUGH LEVEL		
Sequence: Number of subject - Neoral® capsules (N)- Number of blood collection for BTL		
Visit 1	Visit 4	Visit 7
Day -7	Day 18	Day 35
1 st BTL	2 nd BTL	3 rd BTL
*-N-1	*-E-2	*-N-3

* Number of subject

• Pharmacokinetics

A total of twelve 1 mL blood samples will be collected during each 12-hour PK period. A total of three 1 mL blood samples will be collected during each 2-hour sparse sampling PK period. The venous blood samples will be withdrawn at the following times, assuming that the dosing of a subject takes place at 8.00 AM. Sampling schedule:

PHARMACOKINETICS			
Sequence: Number of subject - Neoral® capsules (N) or Equoral capsules (E)- Number of PK - Number of blood collection in PK			
Visit 2	Visit 3	Visit 5	Visit 6
Day 0	Day 14	Day 21	Day 28
C0, C1, C2 - Neoral	PK (12-hour) - Neoral	C0, C1, C2 - Equoral	PK (12-hour)- Equoral
*N-1PK-1	*N-2PK-1	*E-3PK-1	*E-4PK-1
*N-1PK-2	*N-2PK-2	*E-3PK-2	*E-4PK-2
*N-1PK-3	*N-2PK-3	*E-3PK-3	*E-4PK-3
	*N-2PK-4		*E-4PK-4
	*N-2PK-5		*E-4PK-5
	*N-2PK-6		*E-4PK-6
	*N-2PK-7		*E-4PK-7
	*N-2PK-8		*E-4PK-8
	*N-2PK-9		*E-4PK-9
	*N-2PK-10		*E-4PK-10
	*N-2PK-11		*E-4PK-11
	*N-2PK-12		*E-4PK-12

* Number of subject

6.1.1.6. Analytical procedures

Cyclosporine through blood levels will be analyzed by a validated TDx Abbott monoclonal specific antibody methodology in the local Immunoanalytical Laboratories of each particular center involved. The intention to use any analytical method will be consulted first with the CRO Manager of the analytical part (prior to its validation). Finally, the validation of the method will be approved by the CRO Manager of the analytical part before any collection of samples can start.

6.2. ASSESSMENT OF SAFETY

Vital signs, adverse events and laboratory data will be reviewed and medically assessed by the responsible investigator.

A duty doctor will be available within the clinical facility whenever the subjects are housed. A consultant physician will always be available on call during the PK period. Subjects will be questioned for well being at the time of clinical examinations and at the time of recording of vital signs.

6.2.1. Vital signs

The following vital signs will be assessed.

- Body weight (kg)
- Systolic and diastolic blood pressure (mm Hg). Blood pressure will be measured once *always using the same arm* by a trained nurse with a mercury sphygmomanometer in the subjects after they had been sitting quietly for 5 minutes. Method: Riva Rocci, Korotkoff V.
- Radial pulse rate (bpm) after 5 minutes sitting will be measured manually by a trained nurse at the same time
- Body temperature ($^{\circ}$ C)

The vital signs will be assessed and recorded in the CRF at the following times.

Screening: Day -7

Study period I: Day 0, 13, 14

Study period II: Day 15, 18, 21, 27, 28

Study period III: Day 29, 35

6.2.2. Adverse events

Adverse events are illnesses or signs or symptoms that appear or worsen during the course of the study. All adverse events, including observed, elicited, or volunteered problems, complaints or symptoms, are to be recorded on the Adverse Events Case Report Form. The need to capture this information is not dependent upon whether adverse events are associated with the study medication. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications or progression of disease states are also to be recorded. In order to avoid vague, ambiguous or colloquial expressions, adverse events should be recorded in standard medical terminology rather than the subject's own words. Symptoms should be reported individually unless, in the judgment of the Principal Investigator, they can be grouped under an inclusive term (e.g., flu-like symptoms). Each adverse event is to be evaluated for date/time of

Neoral® capsules/ Equoral capsules

Study No.:53/EQ/01/PK
CT I phase

onset, duration, intensity, seriousness and causal relationship with the clinical study material or other factors.

Intensity

The intensity of an adverse event will be characterized as a mild, moderate or severe:

Mild

Transient, require no special treatment, and do not interfere with the subject/subject's daily activities.

Moderate

Introduce a low level of inconvenience or concern to the subject/subject's and may interfere with daily activities, but usually are ameliorated by simple therapeutic measures.

Severe

Interrupt a subject/subject's usual daily activity and require systemic drug therapy or other treatment.

When the intensity of an adverse event changes more than once a day, the maximum severity for the event should be listed. If the intensity category changes over a number of days, then these mini-events or changes should be recorded separately (i.e., having distinct onset dates).

Causality

The causal relationship of the clinical study material to the adverse event will be characterized.

Definition of Relationship to study treatment according to Karch and Casagna.⁶

Definite:

A reaction that follows a reasonable temporal sequence from administration of the investigatory study medication or in which the medication level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected investigatory study medication, and that is confirmed by improvement on stopping the dosage of the investigatory study medication, with reappearance of the reaction on repeated exposure (rechallenge)

Necor® capsules/ Equoral capsules

Study No.:53/EQ/01/PK
CT1.phase

Probable: A reaction that follows a reasonable temporal sequence from administration of the investigatory study medication, that follows a known or expected response pattern to the suspected investigatory study medication, that is confirmed by stopping the dosage of the investigatory study medication, and that could not be reasonably explained by the known characteristics of the patient's clinical state

Possible: a reaction that follows a reasonable temporal sequence from administration of the investigatory study medication, that follows a known or expected response pattern to the suspected investigatory study medication, but that could readily have been produced by a number of other factors

Not Assessable a relationship for which no evaluation can be made

None: a reaction, for which sufficient information exists to indicate that the etiology is unrelated to the investigatory study medication

Any subject with an adverse event or clinically significant abnormal laboratory test will be followed until the problem resolves or is considered clinically insignificant in view of the subject's pre-existing condition. All serious and unexpected adverse events (whether or not related to the study medication and including death due to any cause) that occur during the investigation, must be reported immediately by telephone (within 24 hours) to

CRO MONITOR:

.....
TransMed S.A.L.
Ain Mreissch, Phoenixia St., Sout 3rd,
Beirut, Lebanon
Telephone No.:
Fax No.:
24 Hour Emergency No.:

CRO monitor must report immediately by telephone (within 24 hours) to

IVAX-CR CLINICAL TRIAL MANAGER AND SUPERVISOR OF THE STUDY

Eva Kopečná, MD
Clinical Department of R&D, Galena a.s., Ostravská 29
747 70 Opava-Komárov, Czech Republic
Phone : +420 - 653 - 642639 , Fax : +420 - 653- 642649
Mobil: +420 - 0602 - 583 353
E-mail: eva_kopecná@ivax-cr.com

Neoral® capsules/ Equoral capsules

Study No.: 53/EC/01/PK
CT I phase

The telephone report of the adverse event must contain all available information in order to permit to assess the event. The telephone report should be followed by a full report to include copies of relevant hospital records, autopsy reports and other documents where applicable. Those adverse events of a less serious nature will be reported in writing in the study report.

Following-up adverse events

Investigators should follow-up patients with adverse events until the events have subsided (disappeared) or until the condition has stabilized. Reports relative to the patient's subsequent course must be submitted to the clinical trial monitor.

Overdose

Any instance of over-dosage (suspected or confirmed) must be communicated to the sponsor within 24 hours and fully documented similar to a serious adverse event. Details of any signs or symptoms and their management should be recorded including details.

Pregnancy

Subjects who become pregnant during the study must discontinue the study immediately. Subjects should be instructed to notify the investigator if, after completion of the study they became pregnant:

Either during treatment phase of study

- Or within 30 days or five half-lives after the end of the treatment period, whichever is longer
- Whenever possible a pregnancy test should be followed to term, any premature termination should be reported, and the status of the mother and child should be reported to the sponsor after delivery.

The AES will be assessed and recorded in the CRF at the following times.

Screening: Day -7

Study period I: Day 0, 13, 14

Study period II: Day 15, 18, 21, 27, 28

Study period III: Day 29, 35

6.2.3. Laboratory tests

The Principal Investigator prior to the study initiation must provide the valid normal values for laboratory test results. The Principal Investigator should use the same clinical laboratory

throughout the course of the study and should notify the Study Monitor as soon as possible if normal laboratory test ranges are revised at any time during the study.

The investigator will ensure that the laboratory tests are carried out and that all results are recorded properly. Blood samples will be taken in the fasting state. In general, additional test or repeat test should be performed only if question arises, or following a protocol amendment, or if the laboratory results are aberrant and clinically relevant. It is the investigator's responsibility to document additional tests. The laboratory assessments, evaluation (clinical chemistry, hematology, urine chemistry, and pregnancy test) will be performed in the laboratory of the respective clinic.

Hematology:

Screening: Day -7

Study period II: Day 21

Hemoglobin, Hematocrit, RBC count, WBC count with differential, platelet count

Biochemistry:

Screening: Day -7

Study period II: Day 21

Creatinine, urea, uric acid, calcium, sodium, potassium, chloride, magnesium, inorganic phosphate, alkaline phosphatase (ALP), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), glutamic-pyruvate transaminase (GMT), total bilirubin, amylase, total protein, blood glucose, triglycerides, total cholesterol.

Hematology and biochemistry examinations will be made from approx. 6 mL blood samples.

Urinalysis:

Screening: Day -7

Study period II: Day 21

Protein, glucose, hemoglobin, bile (urobilinogen), acetone (ketone), pH and amylase.

The examinations will be made from approx. 20mL urine midstream urine samples.

Pregnancy

Screening: Day -7 (Pregnancy test in pre-menopausal women of childbearing potential).

Results of all clinically significant abnormal laboratory tests, as identified by the Principal Investigator, should be recorded in the Adverse Events Form of the appropriate Case Report Form. The investigator should indicate and record their clinical significance and relationship to treatment.

7. DATA ANALYSIS METHODS /STATISTICS

7.1. STATISTICAL EVALUATION

7.1.1. Primary endpoints

As the primary endpoints the following steady-state extent and rate pharmacokinetic parameters correlated for the dose (AUC_τ, Peak-trough-fluctuation, C_{min-ss}, C_{max-ss}) and their variabilities will be assessed before and after the switch 1:1 (milligram: milligram) from Neoral capsules to Equoral capsules in stable kidney transplant patients based on standard criteria.

Pharmacokinetic parameters

The pharmacokinetic parameters will be derived individually for each subject and each phase. The actual time of blood sampling will be taken into consideration; the values below the limit of quantification will not be accepted for the next calculations. The following pharmacokinetic parameters of cyclosporine will be analysed by model independent analysis: ^{9, 11, 13}

Area under the blood concentration/time curve over one steady-state dosing interval: AUC_τ

- Maximum and minimum blood concentration in the dosing interval C_{max-ss}, C_{min-ss}, (taken directly from the blood concentration/time curve)
- Peak-Trough Fluctuation: $PTF = (C_{max-ss} - C_{min-ss}) / C_{av-ss}$, where $C_{av-ss} = AUC_{\tau} / \tau$
- Time point of maximum blood concentration: T_{max}
- Terminal elimination rate constant: λ_z
- Half-life of drug elimination during terminal phase: $t_{1/2L} = \ln 2 / \lambda_z$
- Mean Residence Time : MRT = AUMC/AUC
- Relative bioavailability : $F_{rel} = \text{Mean AUC}_{\tau \text{ test}} / \text{Mean AUC}_{\tau \text{ reference}}$

All extent data will be corrected for the administered dose. The area under the blood concentration-time curve (AUC_τ) will be calculated using linear trapezoidal rule. The elimination rate constant will be estimated using log-linear least squares regression analysis of the terminal part of the blood concentration/time curve.

All results – except T_{max} data – will be given as mean, standard deviation, geometric mean and of 95%-confidence limits, corresponding to mean $\pm t_{\alpha(n-1)} \cdot \text{SEM}$ in the logarithmically transformed domain, i.e. $\exp(\text{mean}[\ln] \pm t_{\alpha(n-1)} \cdot \text{SEM}[\ln])$. Parameter T_{max} will be presented as median and extreme data.¹¹

7.1.2. Analytical plan

Non-compartmental pharmacokinetic analysis of whole blood cyclosporine concentration will be performed by means of KINBES module (version 1.34) of the MW/PHARM software (version 3.30)¹². Statistical calculations will be performed using STATISTICA, version 6 (StatSoft, U.S.A.).

Based on the multiplicative model for both extent and rate characteristics, a natural logarithmic transformation of parameters AUC_t, PTF, C_{max}, and C_{min} prior to data analysis will be performed. In the case of parametric statistical analysis, an analysis of variance (ANOVA) model including subject, treatment-phase, and study centre as factors, will be performed. Non-parametric statistical analysis (Wilcoxon tests) will be used, too.⁹

The following hypothesis will be tested at the 5% significance level as consumer risk: H₀: the test formulation is non-equivalent to the reference, i.e. the mean response μ_T of the test formulation differs by $\delta = (0.22 \text{ for AUC; } 0.36 \text{ for C}_{\max})$ or more from the mean response μ_R to application of the reference: $|\mu_T - \mu_R| \geq \delta$;

H₁: the test formulation is equivalent to the reference, i.e. the mean response μ_T to dosing of the test formulation differs by less than $\delta = 0.22$ from the mean response μ_R to dosing of the reference: $|\mu_T - \mu_R| < \delta$. Consistent with the two one-sided tests, the 90%-confidence intervals will be calculated for each parameter.

The null-hypothesis H₀ will be rejected and the equivalence between test and reference formulation will be concluded, if the 90%-confidence interval for the difference ($\mu_T - \mu_R$) of means is included in the interval -0.22 to 0.22, i.e. the ratio of geometric means (test /reference) is included in the bioequivalence range from 0.80 to 1.25 (AUC_t, PTF, C_{max})^{7, 12}. For highly variable parameter C_{max} (if its coefficient of variability will exceed 30%), the acceptance limits could be widened by Boddy¹⁰ up to range of (0.70, 1.43).

Power of the tests should be 80% or more.

Interim pharmacokinetic analysis is planned with data from 32 patients.

7.1.3. Secondary endpoints

Blood trough levels, C₁ and C₂ will be separately evaluated.

7.1.4. Tertiary endpoints

The treatment group will be described using summary statistics. Demographic characteristics at baseline, drug blood levels, number of dose adjustments, daily doses of cyclosporine, incidence

of adverse events, incidence and severity of known cyclosporine side effects including nephrotoxicity episodes and changes in blood pressure will be analysed using appropriate statistical tests. Newly occurring adverse events will be categorized and listed by treatment group. Laboratory variables will be calculated by non-parametric statistics.

7.2. TARGET SAMPLE SIZE

If the study were a cross-over bioequivalence assessment, based on multiplicative statistical model and following assumptions:

- (i) the real relative bioavailability of the test product between 91 and 110% ,
- (ii) the bioequivalence range between 0.8 and 1.25,
- (iii) the level of significance $\alpha=5\%$,
- (iv) the intra-subject coefficient of variability $CV = 20\%$ ¹³,
- (v) the usually required power of the statistical test $(1 - \beta) = 80\%$,

the sample size necessary for concluding bioequivalence would be approximately 32 subjects ¹⁶.

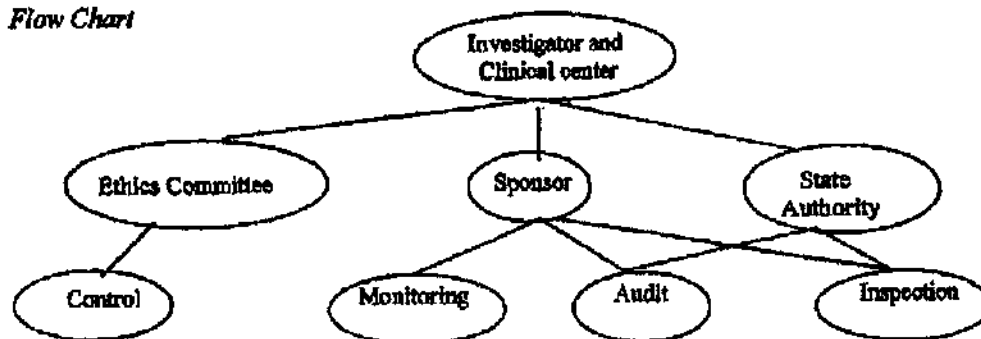
7.3. OUTLIERS

In case of significant violation of inclusion or exclusion criteria affecting or influencing the results of the pharmacokinetics analysis, or if they can not be estimated, the subject will be excluded from the pertaining pharmacokinetics analysis. All subjects who have received at least one dose of the study medication will be included in the safety evaluation.

8. DIRECT ACCESSION TO SOURCE DATA AND DOCUMENTATION

The investigator and clinical centres staff must enable direct accession to the subject's source data and documentation to the persons delegated by National Ethics Committee, Sponsor and Regulatory Authority.

Flow Chart



9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. STUDY MONITORING

CRO TransMed S.A.L. will maintain a close liaison with the Investigator and staff to clarify problems that may arise during the study, and to insure that the investigation is being carried out according to the Protocol. The study will be monitored throughout by the responsible monitor in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and the progress of the study. The monitoring will consist of personal visits before the study is initiated, when the centre is opened, at appropriate intervals during the study and at the end of the study. The monitoring will include also communications via telephone and letter.

The CRO TransMed S.A.L. is responsible according to ICH GCP guidelines for assuring proper study conduct as regards protocol adherence and validity of the data recorded on the CRFs. The monitors of TransMed S.A.L. will assist to the investigator in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, the monitors will ensure that the investigator understands all applicable regulation concerning the clinical evaluation of an investigational drug, as laid down in ICH GCP guidelines.

The investigator agrees to allow the monitor access to the study drug dispensing and storage area and to all clinical data of the study subjects for the above purposes and agrees to assist the monitor in these activities. The investigator accepts that the monitor will visit the clinic at regular intervals to review and verify the data collected. The monitor will regard all information, which is supplied to him or her as strictly confidential. The monitoring visits are for the purpose of verifying adherence to the protocol and for completeness and exactness of data entered in the case report forms and drug inventory forms. The monitor will verify CRF entries by comparing them with the clinic/practice raw data, which will be made available for this purpose. The monitor will retrieve complete CRF sections at each visit. Adequate time and space for these visits should be made available by the investigator.

9.2. DEVIATIONS FROM PROTOCOL

The Investigator shall strictly adhere to the Protocol approved by the Ethics Committee. All deviations from the protocol must be reported to the Monitor. The continued participation of subjects who are protocol violators will be decided by the TransMed S.A.L. clinical trial manager.

Neoral® capsules/ Equoral capsules

Study No.: 53/EQ01/FK
CT I, phase:

Subjects who are not evaluable due to protocol violations that were within the control of the Principal Investigator will not be considered completed subjects.

9.3. DISCONTINUATION OF STUDY

The study may be terminated at any time by TransMed S.A.L. (after agreement with sponsor) or by Sponsor itself if serious or excessive significant side effects should appear; if the Investigator does not adhere to the Protocol; or if, in Sponsor's opinion, there are no further benefits to be achieved from the study. In the event of such termination, the Monitor will inform the Investigator and the appropriate Ethics Committee in writing of the reason for the discontinuation.

9.4. QUALITY ASSURANCE

This study may be subject to audit by Sponsor or local and/or foreign Regulatory Authority. In such case, all relevant information must be available by the responsible investigator and he/she, as well as the involved site personnel, must reserve time for review and discussions of any findings during the audit.

10. REGULATORY AND ETHICAL CONSIDERATIONS

10.1. REGULATORY AUTHORITY APPROVAL

Regulatory requirements from local Regulatory Authority will be met prior to any enrolment of subjects. The responsible investigator is informed about notification of the clinical study to the competent local state authorities.

10.2. ETHICAL CONSIDERATIONS

The study will be conducted in agreement with regulations of the National Ethics Committees according to the following guidelines and directives:

- World Medical Association Declaration of Helsinki 1964 (revised 1975, amended 1983, 1989, 1996 and WMA General Assembly, Edinburgh, Scotland, October 2000)
- International Conference on Harmonization Guidelines for "Good Clinical Practice"
- Good Clinical Practice for Studies on Medicinal Products in the European Community (CPMP) Guidelines.
- All relevant local legal laws including respective drug laws
- Relevant Standard operating procedures (SOP)

State authority and the Ethics committees must be informed by the TransMed S.A.L. of all subsequent protocol amendments (dated, numbered). Approval for such changes must be transmitted in writing to the responsible sponsor's person. Any amendment has to be approved by the Sponsor and has to be signed by the principal investigator. State authority and the Ethics committees will be informed by the TransMed S.A.L. in compliance with the local laws and requirements of all serious and unexpected adverse events and of serious adverse events which change the risk-benefit ratio occurring the study, which are likely affect the safety or the conduct of the study.

10.3. WRITTEN INFORMED CONSENT

Subjects who are asked to participate in clinical research are entitled to choose whether or not to take part. Their decision is voluntary and they should be competent to understand what is involved. Consent forms are designed to assure the protection of subject's rights. Subjects must receive adequate verbal and written information which is in their own language. Either the main investigator or a medically qualified deputy who is a co-worker for the study will perform the verbal explanation to the subject. The verbal explanation will cover all the elements specified in the written information provided for the subject. The investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study including any discomfort it may entail. The subject must be given every opportunity to clarify any points the subject does not understand and if necessary ask for more information. At the end of the interview the subject may be given time to reflect, if this is appropriate. It should be emphasized that the subject is at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. The investigator is responsible for obtaining the subjects' freely given consent. The written consent form provided to the subject should be signed and dated by the subject as well as the investigator. The subject should be given a copy of the document which includes the name and phone number of the person to contact in case of an emergency. The consent must be kept on file by the investigator for possible inspection, monitoring and audit by Regulatory Authorities and/or Sponsor professional persons. The signature confirms the consent which is based on information that has been understood.

10.4. ETHICS COMMITTEE APPROVAL

The investigator or TransMed S.A.L. will submit the appropriate documentation to the National ethics committee for approval prior to any enrolment of subjects. Informed consent form is to be in local language. Details of the methods to be used for recruitment of subjects into the study should also be provided. If, during the study, it is necessary to amend either the protocol or the informed consent form, the investigator will be responsible for ensuring the ethics committee reviews and approves these amended documents.

11. DATA HANDLING, RECORDS KEEPING, ARCHIVING OF DATA, AUDIT

11.1. DATA HANDLING

In accordance with applicable regulatory requirements, following closure of the study, the investigator will maintain a copy of all site study records in a safe and secure location for retaining these records for 15 years.

11.2. ARCHIVING OF DATA

IVAX-CR will archive all necessary source data obtained in the study in accordance with section 4.9.5 of the ICH-GCP Guidelines. The responsible investigator will also archive the source data obtained from the patients, the signed patients informed consent forms and the patients identification records and other essential documents listed in section 8 of the ICH-GCP Guidelines in accordance with section 4.9.5 of the ICH-GCP Guidelines. The original CRF will be kept in the archive of IVAX-CR. The investigator will have a "key" linking the subjects study identification number to the subjects file.

11.3. AUDIT

When an investigator signs the protocol, he agrees to allow a drug regulatory agency and representatives of the sponsor or CRO to inspect his study records. Furthermore, if an investigator refuses an audit/inspection, his data will not be accepted in support a New Drug Registration and/or Application. An audit assesses the quality of data with regard to accuracy, adequacy and consistency. Furthermore audits entail a review of source documents supporting the adequacy and

accuracy of CRF's review of documentation required to be maintained, and checks on drug accountability.

12. INDEMNIFICATION AND COMPENSATION FOR INJURY

TransMed S.A.L. agrees to adhere to the Clinical Study Compensation Guidelines in the event of any injury attributable to participation in this study. In the event that there are any claims against the investigator directly resulting from the administration of this agreed protocol, TransMed S.A.L. will indemnify the investigator on the terms as set out in the indemnification statement.

13. INFORMATION DISCLOSURE AND INVENTIONS

13.1. OWNERSHIP

All data and records provided by IVAX-CR or generated during the study (other than a subject's medical records) and all inventions discovered in the course of conducting the study are the property of IVAX-CR. If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed, that contract's ownership provisions shall apply rather than this statement.

13.2. CONFIDENTIALITY

The investigator and other study site personnel will keep confidential any information provided by IVAX-CR (including this protocol) related to this study and all data and records generated in the course of conducting the study, and will not use the information, data, or records for any purpose other than conducting the study. These restrictions do not apply to:

- information which becomes publicly available through no fault of the investigator or study site personnel
- information which it is necessary to disclose in confidence to an ethics committee solely for the evaluation of the study
- information which it is necessary to disclose in order to provide appropriate medical care to a study subject
- study results which may be published as described in the next paragraph

13.3. PUBLICATION

The principle investigator agrees that information developed during the course of this clinical study or before completion of sponsor's integrated clinical report will be published in agreement

with IVAX-CR Both parties agree that before publishing any results of this study they provide the other party at least 30 days for full review of the pre-publication manuscript. In accordance with generally recognized principles of scientific collaboration, co-authorship with any of IVAX's personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher. Prior to submitting for publication, presenting, using for instructional purposes or otherwise disclosing the results of the study, the investigator shall allow IVAX-CR a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed publication or disclosure prior to its submission for publication or other disclosure. Publications or disclosures of study results shall not include other, confidential information of IVAX-CR

14. DATA MANAGEMENT

Data entry will be performed by Data Management PharmTest s.r.o. The CRFs will be logged in, double data entry will be performed and data will be checked using computerized and manual means to identify problem fields. Queries will be issued, e.g., on missing data, inconsistencies, implausibilities, illegible values and improperly corrected items (e.g., without initials, date of change or a clear reason for change). Answers to queries will be implemented in the database.

Medication names will be coded according to the recent ATC classification.

Adverse events will be coded according to sponsor's coding.

Concomitant and prior diseases will be coded according to ICD-10 coding.

Coding will be done or supervised by medically qualified personnel.

Programmed validation and plausibility checks will be run to check the data and queries will be generated in case of any findings. In addition, a manual/visual check will be performed for medical plausibility. Queries from both processes will be forwarded to the monitor for clarification with the investigator. The data will be corrected according to the results of the queries. Laboratory data will be checked against the laboratory normal ranges. Quality control on the data will be performed on an ongoing basis during the study. Clean data sets will be provided to the statistician to perform the statistical analysis.

14.1. DATA COLLECTION

All data collected on each subject who is enrolled in the study must be noted in the CRF. This should be a complete and accurate record of the subject's data collected during the study. There must be an explanation if it is not possible to collect certain data or if it is missing. The main

investigator at each site is responsible for the quality of the data recorded in the CRF and has therefore to sign and date every CRF after completion.

The investigator or co-investigators must record all required subject data using the previously specified data collection method defined by IVAX-CR. An explanation must be documented for any missing data. The investigator must sign and date a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded and that the data represents a complete and accurate record of each subject's participation in the study.

The following source data will be present in the subject's CRF:

Demography and medical history

Diagnosis

Inclusion/exclusion criteria

Physical examination, vital signs

Laboratory parameters

CyA blood trough levels

Dosing details and blood sampling record

Occurrence of adverse events/serious adverse events

Concomitant medication

Termination of the study

The original copy of all case report forms will be submitted to the Sponsor after being reviewed and signed by the Investigator.

14.2. SOURCE DATA

All source data - family history, anamnesis, demography, physical examination, vitals signs, laboratory notes, dosage of the test and reference drugs, concomitant medication, original recordings from automated instruments, tracings (ECG, EEG), X-ray films, except the data written for the first time in the CRF, must be stored in the subject's medical record.

14.3. DATA RECORDING

In order to facilitate further handling, CRFs should preferably be completed with a black ballpoint. The principal investigator must sign and date the CRF, certifying the accuracy and

Neoral® capsules/ Equoral capsules

Study No.: 53/5Q/01/PK
CT I phase

completeness of the data and that the study was carried out according to the protocol. The instructions for completing the CRF will be place at the beginning of each CRF.

15. STUDY ADMINISTRATION

15.1. SPONSOR STUDY DOCUMENTATION

The following clinical study documents have to be available at TransMed S.A.L.:

1. Original protocol with blank patient information/consent, all appendices and amendments (if necessary), including the original study title – and agreement page and original EC-votes (including up-dates)
2. Blank CRF
3. Investigators brochure (or product information)
4. Copy of the contract signed between the principal and/or responsible investigators and the sponsor
5. Curriculum vitae of the principal investigator and the responsible investigators
6. Declaration of Helsinki (Edinburgh 2000)
7. Original release certificate of the study medication by the sponsor or pharmaceutical manufactures
8. List of study material delivered for the conduct of the study signed by the investigator/monitor
9. Certificate of receipt and return of the medication (drug receipt – and return form)
10. Copy of the announcement and approval of the clinical study to State authority
11. Confirmed copy of the respective Patients Insurance for the clinical study
12. List of the study personnel authorized by the respective responsible investigator
13. Description of clinical laboratory facilities including a list of all normal laboratory ranges, changes in laboratory ranges.
14. Copy of the latest certificates of external QC of the laboratory
15. Copy of the monitoring visit reports: pre-study, during the study course, post end of the study
16. Documentation of the CRF corrections
17. Notification of the serious adverse events
18. Correspondence

15.2. STUDY FILE FOR THE INVESTIGATOR

1. Contact to clinical trial responsible persons
2. Confidentiality disclosure agreement --signed and dated
3. Hospital financial agreement --signed and dated
4. Investigator financial agreement
5. Copy of protocol (final version) - signed and dated
6. Copy of protocol amendments - signed and dated
7. Investigator's Brochure
8. Sample case report form (final version) and correction sheet
9. Subject information sheet
10. Informed consents
11. Copy of the Ethics Committee vote/List of members- signed and dated
12. Declaration of Helsinki (latest version)
13. ICH-GCP guidelines
14. Copy of Regulatory authority approval
15. Curriculum vitae- signed and dated
16. Copy of Certificate of subjects insurance
17. Subject screening/identification list
18. Subject enrollment list
19. Study personal signature sheet
20. Shipping record for study related material
21. Copy of the latest laboratory certificate and reference ranges of laboratory values
22. Investigational product (sponsor analysis certificates of the new drug, sponsor drug release certificate, receipt form, return form, dispensing record, accountability record, destruction form
23. Pre-study visit reports
24. Monitoring Log Form (pre-study, during the study course, at the end of the study)
25. Record of retained biological samples
26. Serious adverse events
27. CRF tracking sheets
28. Completed CRF and correction sheets
29. Correspondence
30. Others

15.3. STUDY AND SITE CLOSURE

Upon completion of the study, the following activities, when applicable, must be conducted by the CRO's monitor in conjunction with the investigator, as appropriate:

- Return of all study data to IVAX-CR a.s
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and non-used study drugs
- Review of site study records for completeness.

In addition, IVAX-CR reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time and for any reason. If such action is taken, IVAX-CR will discuss this with the principal investigator (including the reasons for taking such action) at that time. IVAX-CR will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the ethics committee promptly and provide the reason for the suspension or termination. If the study is prematurely discontinued, all study data must be returned to IVAX-CR. In addition, the site must conduct final disposition of all unused study drugs in accordance with IVAX procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and IVAX-CR.

16. ANTICIPATED DURATION OF STUDY

The study is expected to start in April 2002 and to be completed by the end of June 2002. Each subject will be evaluated in the study for 5 weeks. It is understood that these accrual rates are based on reasonable planning expectations. The investigator should, however, continually compare the actual and expected accrual rates, and make every effort to ensure that they are as closely matched as possible. If the investigator anticipates major problems with recruitment, or delay in the expected completion date, he/she should discuss this with the Clinical Study Monitor as early as possible. If the deadline of the submission of the study report is not fulfilled the sponsor has a right to penalize the clinical centre.

17. RESPONSIBILITIES

Study co-ordinator

Prof. Marvan Masri will be responsible for the medical supervision and will assure that the study will be performed according to local requirements and especially according to the actual EC Notes for Guidance „Good Clinical Practice“.

Supervisor of the study

Eva Kopečná, MD, Clinical Department of R&D, IVAX-CR will be responsible for supervising of the study and for reporting of serious adverse events to the pharmacovigilance department. She will prepare the protocol of the study, CRF, Informed consent form, and Information for Patient form, she will prepare the test and reference medications and arrange for its delivery to the clinical sites.

CRO

TransMed S.A.L. will be responsible for translations of Informed consent form and Information for patient form into local languages, for preparing of Investigator's file, for arranging the insurance for the study, for analytical part of the study, for conducting and monitoring of the study, for filing the related documentation, for reporting of serious adverse events to the supervisor of the study.

Data management

Hana Janská, PharmTest s.r.o. will be responsible for data management of clinical part of the study.

Statistical data analysis and reporting

Josef Šedivý, MD, PhD will be responsible for Statistical data analysis and reporting of the pharmacokinetic parts of the study.

Dalibor Svoboda, PharmTest s.r.o. will be responsible for Statistical data analysis and reporting of the clinical part of the study.

Equoral[®] capsules

16. Appendices

16.1 Study Information

16.1.2 Sample Case Report Form

18. REFERENCES

1. Foulds D, Goa KL, Benfield P. Cyclosporin. A Review of its Pharmacokinetic Properties, and Therapeutic Use in Immunoregulatory Disorders. *Drugs* 1993;45(6):933-1040
2. MICROMEDEX database, Volume 2001
3. Sadeg N, Pham-Huy C, Rucay P, et al. In vitro and in vivo comparative studies on immunosuppressive properties of cyclosporines A, C, D and metabolites M1, M17 and M21. *Immunopharmacol. Immunotox.* 1993;15(2&3):163-177
4. Viaet F. Comparative, randomized, single-dose, 4-way crossover bioavailability of Zenith Goldline, Novartis (NEORAL®), USA) and Sandoz (NBORAL®, UK 100 mg Cyclosporine Soft Gelatin Capsules in Healthy Adult Males Following Administration of a 200 mg Dose under Fed and Fasting Conditions (Phoenix Clinical Research Center, Montreal, Canada; Protocol No.006661). Clinical study report 2000. Data on file, IVAX-CR
5. Will NJ. Comparative, randomized, single dose, 3-way crossover bioavailability study of Zenith, Novartis (Neoral®), and Sandoz (Neoral®) 100 mg cyclosporine Soft Gelatin Capsules in healthy adult males following administration of a 200 mg dose under fasting conditions (Phoenix Clinical Research Center, Montreal, Canada; Protocol No.992216). Clinical study report 2000. Data on file, IVAX-CR
6. Karch, Casagna. Definition of Relationship to study treatment. *J. Am. Med. Assoc.* 1975; 234:1226-1241
7. Kahn BD: Considerations concerning generic formulations of immunosuppressive drugs. *Transplant.Proc.* 1999; 31: 1635-1641
8. Benet LZ: Understanding bioequivalence testing. *Transplant.Proc.* 1999; 31(Suppl. 3A): 7S-9S
9. Sauter R, Steinijans VW, Diletti E, et al. Presentation of results from bioequivalence studies. *Int.J.Clin.Pharmacol.Ther.Tox.* 1992; 30(Suppl.1): S7-S30
10. Boddy AW, Snikeris FC, Kringle RO, et al. An approach for widening the bioequivalence acceptance limits in the case of highly variable drugs. *Pharm. Res.* 1995; 12: 1865-1868
11. FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. FDA/CDER, January 2001 (www.fda.gov/cder/guidance/index.htm)
12. Proost JH, Meijer DKF. MW/PHARM, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring. *Comput.Biol.Med.* 1992; 27(3): 155-163
13. Christians U, Roy First M, Benet LZ. Recommendations for bioequivalence testing of cyclosporine generics revisited. *Ther.Drug Monit.* 2000; 22(3): 330-345
14. Schuurmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J.Pharmacokin.Biopharm.* 1987; 15(6): 657-680
15. Benet LZ: Relevance of pharmacokinetics in narrow therapeutic index drugs. *Transplant.Proc.* 1999; 31: 1642-1644
16. Diletti E, Hauschke D, Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. *Int.J.Clin.Pharmacol.Ther.Tox.* 1992; 30(Suppl.1): S51-S58

Sample Case Report Form

Study No.: 53/EQ/01/PK

Project: Equoral capsules 25 mg, 50 mg, 100 mg

Sponsor: IVAX-CR a.s., Ostravská 29, 747 76 Opava-Komárov, The Czech Republic

CASE REPORT FORM

TITLE OF THE STUDY

A PHARMACOKINETIC CONVERSION STUDY OF EQUORAL (IVAX-CR)
AND NEORAL[®] IN STABLE ADULT RENAL TRANSPLANT RECIPIENTS

SUBJECT'S CODE

Subject Initials
(First name, second name, family name)

Subject No.

Center No.

INVESTIGATOR(S):

STAMP OF TRIAL INSTITUTION:

Neuron[®] capsules/Equoral capsulesStudy No.:53/BQ/01/PK
CT Iphase

TABLE OF CONTENTS

TITLE PAGE.....	1
TABLE OF CONTENTS.....	2
STUDY FLOW CHART.....	4
GENERAL INSTRUCTIONS.....	5
DEFINITION OF ADVERSE EVENTS.....	6

PRE-STUDY SCREENING/VISIT 1

DAY -7

Demography, social history

General medical history

Physical examination, vital signs

Inclusion criteria

Exclusion criteria

Hematology, biochemistry, urinalysis, CyA levels

Baseline medication/treatment

STUDY PERIOD/VISIT 2

DAY 0

Physical examination, vital signs

Baseline events

Concomitant medication/treatment

Checklist of requirements for the study

1st PK (C0, C1, C2) – Blood sampling and dosing record

STUDY PERIOD/VISIT 3

DAY 13

Physical examination, vital signs

Adverse events

Concomitant medication/treatment

DAY 14 – 2nd PK (12-hour)

Vital signs 0 - 4

Vital signs 6 - 10

Blood sampling

Food and liquid intake

Adverse events

Concomitant medication/treatment

Physical examination, vital signs – end of PK

DAY 15

Physical examination, vital signs

Adverse events

Concomitant medication/treatment

STUDY PERIOD/VISIT 4

DAY 18

Physical examination, vital signs, BTL

Adverse events

Concomitant medication/treatment

Neoral® capsules/Equoral capsules

Study No.: 33/EQ/01/PK
CT I phase

STUDY PERIOD/VISIT 5

DAY 21

Physical examination, vital signs

Hematology, biochemistry, urinalysis, CyA levels

Adverse events

Concomitant medication/treatment

3rd PK (C0, C1, C2) – Blood sampling and dosing record

STUDY PERIOD/VISIT 6

DAY 27

Physical examination, vital signs

Adverse events

Concomitant medication/treatment

DAY 28 – 4th PK (12-hour)

Vital signs 0 - 4

Vital signs 6 - 10

Blood sampling

Food and liquid intake

Adverse events

Concomitant medication/treatment

Physical examination, vital signs – end of PK

DAY 29

Physical examination, vital signs

Adverse events

Concomitant medication/treatment

STUDY PERIOD/VISIT 7

DAY 35

Physical examination, vital signs

Adverse events

Concomitant medication/treatment

CyA BTL and dosing record-Summary

Rejection episodes/Rejection therapy-Summary

Study end - Subject completion/withdrawal

Study end - Comments

Study end - Investigator's and monitor's statement

Neoral[®] capsules/Equoral capsulesStudy No.: 53/EQ/01/PK
CT I phase**STUDY FLOW CHART**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Visit	1	2	3	4	5	6	7
Day	-7	0	13	18	21	27	35
General medical history	X						
Demographic data	X						
Physical examination, Vital signs	X	X	X	X	X	X	X
Informed consent	X						
Subject selection criteria	X	X					
Hematology Biochemistry Urine chemistry	X				X		
Pregnancy test (if appropriate)	X						
CsA blood trough level	X			X			X
Adverse events assessment		X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X

12-HOUR PHARMACOKINETICS
(Visit 3/Day 14, Visit 6/Day 28)

Sampling times	Prior to dosing	30min	1h	1h 30 min	2h	3h	4h	5h	6h	8h	10h	12h
Vital signs	X				X		X		X		X	X
Physical examination												X
Adverse events							X					
Concomitant medication							X					
Food and liquid intake							X					

SPARSE SAMPLING (C₀, C₁, C₂) PHARMACOKINETICS
(Visit 2/Day 0, Visit 5/Day 21)

Sparse sampling times	Prior to dosing	1h	2h								

General Instruction for completing these Case Report Forms

- Write clearly, using black biro.
- Press firmly with pen.
- Complete all questions. Do not leave any blank spaces.
- If an error is made:
 - do not use masking fluid
 - draw a single line through the error,
 - write the correct entry in an adjacent space,
 - initial and date the correction.
- If a test is not done, write ND.
- If a test is zero, write 0.
- Please ensure that the patient consent form is signed.
- Please record all concomitant medication.
- Please complete patient's withdrawal/completion form.
- Please inform the study monitor of all protocol deviations.
- Please document all adverse events.

e.g.

1	7	3

 cm
 183 cm
 EK 09.Oct.02

Please notify to monitor of the study within 24 hours of all "serious adverse events"

Monitor:

Telephone No.:

Fax no.:

24-Hour Emergency No.:

e-mail.....

Or

Telephone No.:

Date and time (1st January 2001)

0 1 J A N 2 0 0 1

- Date and time

Complete the date in the following format:

DD	MON	YEAR

- Unless specified otherwise, use the 24 hour clock 00:00 – 23:59

Neoral® capsules/Equoral capsules

Study No.:53/EQ01/PK
CT I phase**Definition of Adverse Events****Definition of Intensity**

Mild	Adverse Experience which is easily tolerated.
Moderate	Adverse Experience sufficiently discomforting or interfere with daily activity
Severe	Adverse Experience which is incapacitating and prevents normal activity.

**Definition of Relationship to study treatment according to Karch and Casagna
(J. Am. Med Assoc-234; 1226-1241, 1975)**

Definite:	a reaction that follows a reasonable temporal sequence from administration of the investigatory study medication or in which the medication level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected investigatory study medication, and that is confirmed by improvement on stopping the dosage of the investigatory study medication, with reappearance of the reaction on repeated exposure (rechallenge)
Probable:	a reaction that follows a reasonable temporal sequence from administration of the investigatory study medication, that follows a known or expected response pattern to the suspected investigatory study medication, that is confirmed by stopping the dosage of the investigatory study medication, and that could not be reasonably explained by the known characteristics of the patient's clinical state
Possible:	a reaction that follows a reasonable temporal sequence from administration of the investigatory study medication, that follows a known or expected response pattern to the suspected investigatory study medication, but that could readily have been produced by a number of other factors
Not Assessable:	a relationship for which no evaluation can be made
None:	a reaction, for which sufficient information exists to indicate that the aetiology is unrelated to the investigatory study medication

**Use each form for the maximum of two experiences.
All questions on the Adverse events form should be completed.**

PRE-STUDY SCREENING**VISIT 1/ DAY -7**

Neoral® capsules/Equoral capsules

Study No.: 33/EQ/01/PK
CT 1 phase**PRE-STUDY SCREENING VISIT 1/DAY -7**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (VAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 33/EQ/01/PK)

Subject Code				Date					
	Subject Initials	Subject No.	Center No.		Day	Month	Year		

INCLUSION CRITERIA

Participating subjects have to fulfil the following criteria:

Please cross the appropriate box

1. Either sex	☐ yes	☐ no
2. Age: 18-70 years	☐ yes	☐ no
3. First renal transplant (cadaveric or living donor)	☐ yes	☐ no
4. No rejection episode in the past 6 months	☐ yes	☐ no
5. Clinically stable for at least 6 months post transplantation with acceptable safety/tolerance to Sandimmun® Neoral capsules	☐ yes	☐ no
6. Three last consecutive whole blood cyclosporine trough levels in the range of 70- 200 ng/ml (RIA specific)	☐ yes	☐ no
7. Stable serum creatinine in the past 3 months with no trend to increase	☐ yes	☐ no
8. No hepatic dysfunction in the past 6 months (increase of aminotransferase <100% above the baseline)	☐ yes	☐ no
9. No history of alcohol or drug abuse or signs of alcohol-induced organ damage	☐ yes	☐ no
10. No clinical symptoms of CMV infection in the past 6 months	☐ yes	☐ no
11. No history of malignancy or any significant infection	☐ yes	☐ no
12. Blood pressure in normotensive range with or without antihypertensive medication	☐ yes	☐ no
13. Maintained on cyclosporine in double or triple combination with prednisolone, azathioprine, mycophenolate mofetil	☐ yes	☐ no
14. Doses of cyclosporine $\leq$ 8 mg/kg. The dose has to be stable over the previous 15 days prior to entry	☐ yes	☐ no
15. Doses of concomitant medication stable 14 days prior to study entry	☐ yes	☐ no
16. Subject's ability to communicate well with the investigator	☐ yes	☐ no
17. Written informed consent is to be obtained	☐ yes	☐ no
18. Subject has not participated in another clinical trial within 28 days preceding this study	☐ yes	☐ no

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase**PRE-STUDY SCREENING VISIT 1/DAY -7**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

EXCLUSION CRITERIA

Subjects will be excluded if they have any of the following criteria:

Please cross the appropriate box

1. Significant history of hypersensitivity to cyclosporine or any related products	☐ yes	☐ no
2. Significant history of hypersensitivity to castor oil, olive oil or corn oil	☐ yes	☐ no
3. Pregnancy or lactating females	☐ yes	☐ no
4. Premenopausal women of childbearing potential not using safe contraception	☐ yes	☐ no
5. >1 renal transplant or grafts of other organs (e.g. pancreas)	☐ yes	☐ no
6. Use of routine immunosuppressive therapy other than azathioprine, mycophenolate mofetil or prednisol	☐ yes	☐ no
7. Uncontrolled blood pressure (resistant to antihypertensive therapy and despite reduction of cyclosporine dose)	☐ yes	☐ no
8. History of chronic alcoholism, drug or narcotic abuse	☐ yes	☐ no
9. History of myocardial infarction within 6 months of enrollment or uncontrolled cardiac arrhythmia	☐ yes	☐ no
10. History of gastrointestinal illness or any condition which could interfere with absorption of oral medication	☐ yes	☐ no
11. Clinically relevant disease (including nervous system) or other abnormal condition which may compromise function of gastrointestinal tract, kidney or liver or which might influence cyclosporine pharmacokinetics	☐ yes	☐ no
12. Exposition to any drug known to effect cyclosporine blood levels and interfere with cyclosporine pharmacokinetics within 14 days prior to study entry	☐ yes	☐ no
13. Subjects with significant medical problems or unstable disease states	☐ yes	☐ no

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase**PRE-STUDY SCREENING VISIT 1/DAY -7**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

GENERAL MEDICAL HISTORY

Is the subject suffering or has he/she ever suffered from any illness in the following areas?

If yes, please cross the box

1. cardiovascular	☐	8. musculoskeletal	☐
2. respiratory	☐	9. metabolic / nutritional	☐
3. urogenital	☐	10. endocrine	☐
4. gastrointestinal / hepatic	☐	11. neurologic / psychiatric	☐
5. hematologic / immunologic	☐	12. allergy	☐
6. HEENT (head, ears, eyes, nose throat)	☐	13. major surgery	☐
7. dermatologic / connective tissue	☐	14. other	☐

If any answer is YES, please specify with reference to the number:

Ref. Number

Diagnosis

still present

		☐
		☐
		☐
		☐
		☐
		☐
		☐
		☐
		☐
		☐

Investigator's Signature: _____

Neoral[®] capsules/Equoral capsulesStudy No.: 53/EQ01/PK
CT 1 phase**PRE-STUDY PERIOD VISIT 1/DAY -7**Name of the study: A Pharmacokinetic Conversion Study of Equoral (TVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
Head	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNSMeasurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study!

Time of the test	Arm used:	☐ right	☐ left
Hr			
mm			
	Radial pulse rate	Blood pressure	
	(bpm)	Systolic	Diastolic
		(mmHg)	(mmHg)
Body temperature			
	°C		
Body weight:			
	Kg		

Investigator's Signature: _____

PRE-STUDY SCREENING VISIT 1/DAY -7

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

DEMOGRAPHY

Sex

☐ Male☐ Female

Date of Birth

DD

MON

YY

Race

☐ Caucasian☐ Asian☐ Black☐ Oriental☐ Other, please specify: _____

Height

Centimeter

Weight

Kg

SOCIAL HISTORY

Smoking

☐ Yes☐ No

Please specify quantity and duration: _____

Alcohol

☐ Yes☐ No

Please specify weekly quantity: _____

Investigator's Signature: _____

PRE-STUDY SCREENING VISIT 1/DAY -7Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Date

Subject's Initials

Subject No:

Center No:

Day

Month

Year

Investigator's appreciation

HEMATOLOGY	Unit	Value	*	Comments
Hematocrit	%			
Hemoglobin	g/dL			
Erythrocytes	$10^{12}/L$			
Total leukocyte count	$10^9/L$			
Neutrophils	%			
Basophils	%			
Eosinophils	%			
Lymphocytes	%			
Monocytes	%			
Platelets	$10^9/L$			
BIOCHEMISTRY	Unit	Value	*	Comments
S creatinine	umol/L			
S urea	mmol/L			
S uric acid	mmol/L			
S ALAT = SGPT	mkat/L			
S ASAT = SGOT	mkat/L			
S GMT	mkat/L			
S ALP	mkat/L			
S total bilirubin	umol/L			
S amylase	umol/L			
S protein	g/L			
S glucose	mmol/L			
S sodium	mmol/L			
S potassium	mmol/L			
S magnesium	mmol/L			
S chloride	mmol/L			
S calcium	mmol/L			
S phosphorus	mmol/L			
S triglycerides	mmol/L			
S total cholesterol	mmol/L			
URINALYSIS	Unit	Value	*	Comments
pH				
U protein	neg			
U glucose	neg			
U hemoglobin	neg			
U bile (urobilinogen)	neg			
U acetone (ketone)	neg			
U amylase	umol/L			
Pregnancy test	neg			Only in women of child-bearing potential
CsA trough level	Unit			Comments
Dose	mg/d			
Value	ng/mL			

* 0 - value is normal ranges; 1 - no clinically significant abnormal value; 2 - clinically significant abnormal value

Investigator's Signature :

PRE-STUDY SCREENING VISIT 1/DAY -7

Name of the study: A Pharmacovigilance Consortium Study of Enteral (VAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: EQ011PK)

Subject Code	Collected Month	Collected Year	Day	Month	Year

BASELINE MEDICATION / TREATMENT

Phase record on this form details of all medication given to the patient during the pre-study course.

Indication/Diagnosis	Route	Cause
Please, specify according to international classification of diseases (ICD)	1 = oral	1 = study indication
	2 = s.c.	2 = concomitant disease
	3 = i.m.	3 = adverse event (specify in the form "Adverse Events"
	4 = i.v.	5 = treatment of rejection
	8 = inhaled	5 = others, specify in the form "Comments"

[illegible]

Investigator's Signature: _____

STUDY PERIOD

VISIT 2/ DAY 0

Neoral[®] capsules/Equoral capsules

Study No.: 53/EQ/01/PK

CT Phase

STUDY PERIOD VISIT 2/DAY 0Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
lead	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

 Time of the test
 Hr mm
Arm used: ☐ right ☐ left
 Radial pulse rate
 (bpm)

 Blood pressure
 Systolic / Diastolic
 (mmHg) (mmHg)
 /
Body temperature °CBody weight: Kg

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK

CT I phase

STUDY PERIOD VISIT 2/DAY 0

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

BASELINE EVENTSRecord any adverse event observed or elicited by the following direct question to the Subject:
"Have you felt different in any way over the last few days":☐ Yes☐ No

If Yes, please complete one column per one event.

	Event observed	Event observed
Describe		
Onset date	 DAY MONTH YEAR	 DAY MONTH YEAR
End date	 DAY MONTH YEAR	 DAY MONTH YEAR
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action taken	☐ none ☐ concomitant medication/ therapy changed or stopped ☐ others, please specify	☐ none ☐ concomitant medication/ therapy changed or stopped ☐ others, please specify
Outcome	☐ recovered ☐ ongoing ☐ recovered with sequelae	☐ recovered ☐ ongoing ☐ recovered with sequelae

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase**STUDY PERIOD VISIT 2/DAY 0**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No. 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

CHECKLIST OF REQUIREMENTS FOR THE STUDY

Please, cross the appropriate box

1. Have all the tests listed in the Protocol been completed?
If not, discuss ☐ yes ☐ no
1. Has a physical examination been performed? ☐ yes ☐ no
2. Has a medical questionnaire been completed? ☐ yes ☐ no
3. Have the biochemistry, hematology and urine chemistry been completed? ☐ yes ☐ no
4. Have the inclusion criteria in the protocol been met? ☐ yes ☐ no
5. Have the exclusion criteria in the protocol been met? ☐ yes ☐ no
6. Has the „Baseline Medication/Treatment“ form been completed? ☐ yes ☐ no
7. Were all the last three whole blood CyA trough levels within 70- 200 ng/mL ☐ yes ☐ no
8. Has informed consent been signed? ☐ yes ☐ no
9. Has an independent ethical committee approved the protocol? ☐ yes ☐ no

Only in pre-menopausal women of childbearing potential!

10. Was the pregnancy test negative?

☐ yes ☐ no

CsA level from the day - 7: ng/mL

Subject enrolled into the study

☐ yes ☐ no

Morning dose of Neoral® capsules on the day 1: mg

I confirm that all the conditions listed above were met prior to the enrollment to the study.

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.:53/EQ/01/PK
CT I phase**STUDY PERIOD VISIT 2/DAY 0**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

1st PK (C0,C1,C2)- BLOOD SAMPLING AND DOSING RECORD

Product given: Neoral® capsules

Morning dose.....

Dosed at:.....h

Issued by:..... (to be initialed by person administering the dose)

TIME AFTER DOSING
SAMPLE TO BE
TAKEN (HOURS)EXPECTED
TIME FOR
SAMPLETIME
DEVIATION☐

If yes, specify

LABELING
OF THE
SAMPLEAUTHEN.
BY
Initials

0

☐

*-N-2PK-1

1.0 h

☐

*-N-2PK-2

2.0 h

☐

*-N-2PK-3

*Number of subject

Investigator's Signature: _____

STUDY PERIOD
VISIT 3/ DAY 13-15

Neoral[®] capsules/Equoral capsulesStudy No.: 53/EQ/01/PK
CT Phase**STUDY PERIOD VISIT 3/DAY 13**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
Head	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Time of the test

Hr

mm

Arm used: ☐ right ☐ leftRadial pulse rate
(bpm)

Blood pressure

Systolic / Diastolic
(mmHg) (mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.:53/EQ/01/PK

CTI, please

STUDY PERIOD VISIT 3/DAY 14

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)

Subject Code Date

Subject Initials Subject No. Center No. Day Month Year

2nd PK - VITAL SIGNS**Prior to dosing**

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used: ☐ right ☐ left

Time of test		Pulse	Blood pressure	
hh	mm	(bpm)	Systolic	Diastolic
			(mmHg)	(mmHg)

Investigator's/Nurse's Signature : _____

Prior to 2 hr blood collection

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used: ☐ right ☐ left

Time of test		Pulse	Blood pressure	
Hh	mm	(bpm)	Systolic	Diastolic
			(mmHg)	(mmHg)

Investigator's/Nurse's Signature : _____

Prior to 4 hr blood collection

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used: ☐ right ☐ left

Time of test		Pulse	Blood pressure	
hh	mm	(bpm)	Systolic	Diastolic
			(mmHg)	(mmHg)

Investigator's/Nurse's Signature : _____

STUDY PERIOD VISIT 3/DAY 14

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)

Subject Code Date
Subject Initials Subject No. Center No. Day Month Year

2nd PK - VITAL SIGNS

Prior to 6 hr blood collection

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used: ☐ right ☐ left

Time of test		Pulse	Blood pressure	
hh	mm	(bpm)	Systolic	Diastolic
			(mmHg)	(mmHg)

Investigator's/Nurse's Signature : _____

Prior to 10 hr blood collection

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used: ☐ right ☐ left

Time of test		Pulse	Blood pressure	
hh	mm	(bpm)	Systolic	Diastolic
			(mmHg)	(mmHg)

Investigator's/Nurse's Signature : _____

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used: ☐ right ☐ left

Time of test		Pulse	Blood pressure	
hh	mm	(bpm)	Systolic	Diastolic
			(mmHg)	(mmHg)

Investigator's/Nurse's Signature : _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT 1 phase**STUDY PERIOD VISIT 3/DAY 14**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

2nd PK - BLOOD SAMPLING AND DOSING RECORD

Product given: Neoral® capsules

Morning dose.....

Dosed at.....h

Issued by:..... (to be initialed by person administering the dose)

TIME AFTER DOSING
SAMPLE TO BE
TAKEN (HOURS)EXPECTED
TIME FOR
SAMPLETIME
DEVIATION☐

no If yes, specify

LABELING
OF THE
SAMPLEAUTHEN.
BY
Initials

0

☐

*-N-2PK-1

0.5 h

☐

*-N-2PK-2

1.0 h

☐

*-N-2PK-3

1.5 h

☐

*-N-2PK-4

2.0 h

☐

*-N-2PK-5

3.0 h

☐

*-N-2PK-6

4.0 h

☐

*-N-2PK-7

5.0 h

☐

*-N-2PK-8

6.0 h

☐

*-N-2PK-9

8.0 h

☐

*-N-2PK-10

10.0 h

☐

*-N-2PK-11

12.0 h

☐

*-N-2PK-12

*Number of subject

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 13/EQ/01/PK

CT Phase

STUDY PERIOD VISIT 3/DAY 14

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 13/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

2nd PK - FOOD AND LIQUID INTAKE

TIME

FOOD or LIQUID TAKEN

APPROXIMATE QUANTITY

Investigator's Signature: _____

Date: _____

STUDY PERIOD		VISIT 3/DAY 14	
Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neuralt [®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)			
Subject Code			

Name of the study: A Pharmacokinetic Comparison Study of Equival (VAX-CR) and Neutrol® in Stable Adult Renal Transplant Recipients (Study/No...63/EQ1017P1Q)

Subject Code **Subject No:** **Center No:**

Subject / Initials **Day** **Month** **Year**

2nd PK CONCOMITANT MEDICATION / TREATMENT

Has the concomitant medication changed since the day 13? ☐ Yes ☐ No Please cross the appropriate box.

Please record on this form details of all changed medication given to the patient during the PK study period.

Indications/Diagnoses	Route	Cause
1 = oral	5 = rectal	1 = study indication
2 = s.c.	6 = dermal	2 = concomitant disease
3 = i.m.	7 = nasal	3 = adverse event (specify in the form "Adverse Events")
4 = i.v.	8 = inhaled	6 = treatment of rejection
		5 = others, specify in the form "Comments"

[illegible]

Investigator's Signature:

Neoral® capsules/Equoral capsules

Study No.:53/EQ/01/PK

CTI phase

STUDY PERIOD VISIT 3/DAY 14

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)

Subject Code Date

Subject Initials Subject No. Center No. Day Month Year

2nd PK - PHYSICAL EXAMINATION - 12 hr after dosing

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
Head	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS- 12 hr after dosing

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Time of the test
Hr mm

Arm used: ☐ right ☐ left

Radial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg) Diastolic
(mmHg) Body temperature °CBody weight: Kg

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT1 phase**STUDY PERIOD VISIT 3/DAY 15**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Date

Subject Initials

Subject No.

Center No.

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
lead	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Time of the test

Hr mm

Arm used: ☐ right ☐ leftRadial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg)Diastolic
(mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code Subject Initials Subject No. Center No. Date Day Month Year

ADVERSE EVENTS

Please record any observed adverse event since the day 14. Complete one column per one event and cross the appropriate box.

	Event observed	Event observed
Describe		
Onset time	DAY MONTH YEAR	DAY MONTH YEAR
End time	DAY MONTH YEAR	DAY MONTH YEAR
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Appearance	☐ Isolated ☐ Intermittent ☐ Continuous	☐ Isolated ☐ Intermittent ☐ Continuous
Serious ^m	☐ Yes ☐ No	☐ Yes ☐ No
Event causality	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug
Relation to the test drug	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible
Action taken (concerning study drug dose)	☐ None ☐ Dose interrupted/ restarted ☐ Dosedecreased ☐ Drug stopped	☐ None ☐ Dose interrupted/ restarted ☐ Dosedecreased ☐ Drug stopped
Action taken (concerning therapeutic medication)	☐ Yes* ☐ No	☐ Yes* ☐ No
Outcome	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae

* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form.

* According to the protocol serious is defined as fatal, life-threatening, permanently or temporarily disabling, requires inpatient hospitalization or prolongation of hospitalization, or is associated with congenital abnormality, cancer or overdose (either intentional or accidental). For any adverse event treated as serious, contact study monitor and fill in "SERIOUS ADVERSE EVENT REPORT"

Investigator's Signature: _____

STUDY PERIOD VISIT 3/DAY 15

Name of the study: A Pharmacokinetic Conversion Study of Equival (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 33/EQ011/PK)

Subject Code

Subject Initials **Subject No:** **Center No:**

CONCOMITANT MEDICATION / TREATMENT

Yes ☐ **No** ☐ Please circle the appropriate box.

Please record on this form details of all changed medication since the day 14.

1 = study indication
2 = concomitant disease
3 = adverse event (specify)
5 = treatment of rejection
5 = others, specify in the free text

Indication/diagnosis
Please, specify according to
international classification of diseases
(ICD)

Specialists

Trade name
and strength

Done
Total daily

Start Date**End Date**

Continuing?

Investigator's Signature: _____

STUDY PERIOD

VISIT 4/ DAY 18

STUDY PERIOD VISIT 4/DAY 18

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
Head	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Arm used: ☐ right ☐ left

Time of the test

Hr

mm

Radial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg)Diastolic
(mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

STUDY PERIOD VISIT 4/DAY 18

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No. 53/EQ/01/PK)

Subject Code

Subject initials

Subject No.

Center No.

Date _____

Day

Month

YEAR

ADVERSE EVENTS

Please record any observed adverse event since the day 15. Complete one column per one event and cross the appropriate box.

	Event observed	Event observed
Describe		
Onset time	DAY MONTH YEAR	DAY MONTH YEAR
End time	DAY MONTH YEAR	DAY MONTH YEAR
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Appearance	☐ Isolated ☐ Intermittent ☐ Continuous	☐ Isolated ☐ Intermittent ☐ Continuous
Serious**	☐ Yes ☐ No	☐ Yes ☐ No
Event causality	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug
Relation to the test drug	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible
Action taken (concerning study drug dose)	☐ None ☐ Dose interrupted/ restarted ☐ Dose reduced ☐ Drug stopped ☐ Dose increased	☐ None ☐ Dose interrupted/ restarted ☐ Dose reduced ☐ Drug stopped ☐ Dose increased
Action taken (concerning therapeutic medication)	☐ Yes* ☐ No	☐ Yes* ☐ No
Outcome	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae

* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form.

* According to the protocol serious is defined as fatal, life-threatening, permanently or temporarily disabling, requires inpatient hospitalization or prolongation of hospitalization, or is associated with congenital abnormality, cancer or overdose (either intentional or accidental). For any adverse event treated as serious, contact study monitor and fill in "SERIOUS ADVERSE EVENT REPORT".

Investigator's Signature: _____

STUDY PERIOD

VISIT 5/ DAY 21

Neoral[®] capsules/Equoral capsuleStudy No.: 53/EQ/01/PK
CTL phase**STUDY PERIOD VISIT 6/DAY 21**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
Head	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Arm used: ☐ right ☐ left

Time of the test

Hr

mm

Radial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg)Diastolic
(mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

STUDY PERIOD VISIT 5/DAY 21

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No. _____

Date _____

Day

Month

YEAR

ADVERSE EVENTS

Please record any observed adverse event since the day 18. Complete one column per one event and cross the appropriate box.

	Event observed	Event observed
Describe		
Onset time	DAY MONTH YEAR	DAY MONTH YEAR
End time	DAY MONTH YEAR	DAY MONTH YEAR
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Appearance	☐ Isolated ☐ Intermittent ☐ Continuous	☐ Isolated ☐ Intermittent ☐ Continuous
Serious**	☐ Yes ☐ No	☐ Yes ☐ No
Event causality	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug
Relation to the test drug	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible
Action taken (concerning study drug dose)	☐ None ☐ Dose interrupted/ ☐ Dosereduced restarted ☐ Doseincreased ☐ Drug stopped	☐ None ☐ Dose interrupted/ ☐ Dosereduced restarted ☐ Doseincreased ☐ Drug stopped
Action taken (concerning therapeutic medication)	☐ Yes* ☐ No	☐ Yes* ☐ No
Outcome	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae

* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form.

* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form.
 ** According to the protocol serious is defined as fatal, life-threatening, permanent or temporarily disabling, requires inpatient hospitalization or prolongation of hospitalization, or is associated with congenital abnormality, cancer or overdose (either intentional or accidental). For any adverse event treated as serious, contact study monitor and fill in "SERIOUS ADVERSE EVENT REPORT".

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT Phase**STUDY PERIOD VISIT 5/DAY 21**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

3rd PK (C0,C1,C2)- BLOOD SAMPLING AND DOSING RECORD

Product given: Equoral capsules

Morning dose.....

Dosed at:.....h

Issued by:..... (to be initialed by person administering the dose)

TIME AFTER DOSING
SAMPLE TO BE
TAKEN (HOURS)EXPECTED
TIME FOR
SAMPLETIME
DEVIATION☐

no if yes, specify

LABELING
OF THE
SAMPLEAUTHEN.
BY
Initials

0

1.0 h

2.0 h

☐☐☐

*E-3PK-1

*E-3PK-2

*E-3PK-3

*Number of subject

Investigator's Signature: _____

Neoral® capsules/Equoral® capsules

Study No.: 13/EQ/01/PK
1. phase**STUDY PERIOD VISIT 5/DAY 21**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 13/EQ/01/PK)

Subject Code

Date

Subject's Initials

Subject No:

Center No:

Day

Month

Year

Investigator's appreciation

HEMATOLOGY	Unit	Value	*	Comments
Hematocrit	%			
Hemoglobin	g/dL			
Erythrocytes	$10^{12}/L$			
Total leukocyte count	$10^9/L$			
Neutrophils	%			
Basophils	%			
Eosinophils	%			
Lymphocytes	%			
Monocytes	%			
Platelets	$10^9/L$			
BIOCHEMISTRY	Unit	Value	*	Comments
S creatinine	umol/L			
S urea	mmol/L			
S uric acid	mmol/L			
S ALAT = SGPT	mkat/L			
S ASAT = SGOT	mkat/L			
S GMT	mkat/L			
S ALP	mkat/L			
S total bilirubin	umol/L			
S amylase	umol/L			
S protein	g/L			
S glucose	mmol/L			
S sodium	mmol/L			
S potassium	mmol/L			
S magnesium	mmol/L			
S chloride	mmol/L			
S calcium	mmol/L			
S phosphorus	mmol/L			
S triglycerides	mmol/L			
S total cholesterol	mmol/L			
URINALYSIS	Unit	Value	*	Comments
pH				
U protein	neg			
U glucose	neg			
U hemoglobin	neg			
U bile (urobilinogen)	neg			
U acetone (ketone)	neg			
U amylase	umol/L			
Pregnancy test	neg			Only in women of child-bearing potential
CsA trough level	Unit			Comments
Dose	mg/d			
Value	ng/mL			

* 0 - value in normal ranges; 1 - no clinically significant abnormal value; 2 - clinically significant abnormal value

Investigator's Signature :

STUDY PERIOD VISIT 5/DAY 21

Abstract

Subject Code

Subject Initials: _____ Subject No: _____ Center No: _____

CONCOMITANT MEDICATION / TREATMENT

Please email the appropriate box.

Has the concomitant medication changed since the day 18 ?

PLEASE RECORD ON THIS FORM DETAILS OF ALL CHANGED MEDICATION SINCE THE DAY 12.

Route

Indication/Prognosis

on Bajpur Road, Agartala, West Bengal

International classification of diseases

100

Case

2 = conditum disease

3 = advance event (spc)

5 = Fragment of rejection

5 = others, specify in the form "Comments"

Diagnosis

23

Trade name
and strength

Total daily dose	mg/kg

Results

Start Date**End Data**

Continuing?

Investigator's Signature:

STUDY PERIOD
VISIT 6/ DAY 27-29

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT 1 phase

STUDY PERIOD VISIT 6/DAY 27

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
lead	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Arm used: ☐ right ☐ left

Time of the test

Hr

mm

Radial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg)Diastolic
(mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

Subject Code Date

Subject Initials Subject No. Center No. Day Month Year

ADVERSE EVENTS

Please record any observed adverse event since the day 21. Complete one column per one event and cross the appropriate box.

	Event observed	Event observed
Describe		
Onset time	DAY MONTH YEAR	DAY MONTH YEAR
End time	DAY MONTH YEAR	DAY MONTH YEAR
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Appearance	☐ Isolated ☐ Intermittent ☐ Continuous	☐ Isolated ☐ Intermittent ☐ Continuous
Serious**	☐ Yes ☐ No	☐ Yes ☐ No
Event causality	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug
Relation to the test drug	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible
Action taken (concerning study drug dose)	☐ None ☐ Dose interrupted/ restarted ☐ Dosed reduced ☐ Drug stopped ☐ Dose increased	☐ None ☐ Dose interrupted/ restarted ☐ Dosed reduced ☐ Drug stopped ☐ Dose increased
Action taken (concerning therapeutic medication)	☐ Yes* ☐ No	☐ Yes* ☐ No
Outcome	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae

* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form.

** According to the protocol serious is defined as fatal, life-threatening, permanently or temporarily disabling, requires inpatient hospitalization or prolongation of hospitalization, or is associated with congenital abnormality, cancer or overdose (either intentional or accidental). For any adverse event treated as serious, contact study monitor and fill in "SERIOUS ADVERSE EVENT REPORT".

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase**STUDY PERIOD VISIT 6/DAY 28**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

4th PK – VITAL SIGNS**Prior to dosing**Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used:

☐ right☐ leftTime of test
hh : mmPulse
(bpm)Systolic
(mmHg)Blood pressure
Diastolic
(mmHg)

Investigator's/Nurse's Signature : _____

Prior to 2 hr blood collectionMeasurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used:

☐ right☐ leftTime of test
hh : mmPulse
(bpm)Systolic
(mmHg)Blood pressure
Diastolic
(mmHg)

Investigator's/Nurse's Signature : _____

Prior to 4 hr blood collectionMeasurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used:

☐ right☐ leftTime of test
hh : mmPulse
(bpm)Systolic
(mmHg)Blood pressure
Diastolic
(mmHg)

Investigator's/Nurse's Signature : _____

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase**STUDY PERIOD VISIT 6/DAY 28**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

4th PK - VITAL SIGNS**Prior to 6 hr blood collection**Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used:

☐ right☐ leftTime of test
hh : mmPulse
(bpm)Systolic
(mmHg)

Blood pressure

/ Diastolic
(mmHg)

Investigator's/Nurse's Signature : _____

Prior to 10 hr blood collectionMeasurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used:

☐ right☐ leftTime of test
Hh : mmPulse
(bpm)Systolic
(mmHg)

Blood pressure

/ Diastolic
(mmHg)

Investigator's/Nurse's Signature : _____

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.
Please use the same arm for each measurement throughout the study.

Arm used:

☐ right☐ leftTime of test
hh : mmPulse
(bpm)Systolic
(mmHg)

Blood pressure

/ Diastolic
(mmHg)

Investigator's/Nurse's Signature : _____

Neoral[®] capsules/Equoral capsules

Study No.:53/EQ/01/PK

CT Phase

STUDY PERIOD VISIT 6/DAY 28Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

4th PK - BLOOD SAMPLING AND DOSING RECORD

Product given: Equoral capsules

Morning dose.....

Dosed at:.....h

Issued by:..... (to be initialed by person administering the dose)

TIME AFTER DOSING SAMPLE TO BE TAKEN (HOURS)	EXPECTED TIME FOR SAMPLE	TIME DEVIATION	LABELING OF THE SAMPLE	AUTHEN. BY Initials
		☐ no		
		☐ If yes, specify		
0		☐	*-E-4PK-1	
0.5 h		☐	*-E-4PK-2	
1.0 h		☐	*-E-4PK-3	
1.5 h		☐	*-E-4PK-4	
2.0 h		☐	*-E-4PK-5	
3.0 h		☐	*-E-4PK-6	
4.0 h		☐	*-E-4PK-7	
5.0 h		☐	*-E-4PK-8	
6.0 h		☐	*-E-4PK-9	
8.0 h		☐	*-E-4PK-10	
10.0 h		☐	*-E-4PK-11	
12.0 h		☐	*-E-4PK-12	

*Number of subject

Investigator's Signature: _____

Neoral[®] capsules/Equoral capsulesStudy No.: 53/EQ/01/PK
CT I phase**STUDY PERIOD VISIT 6/DAY 28**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

4th PK - FOOD AND LIQUID INTAKE

TIME

FOOD or LIQUID TAKEN

APPROXIMATE QUANTITY

Investigator's Signature: _____

Date: _____

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No. 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date:

Day

Month

Year

4th PK - ADVERSE EVENTS

Please record any observed adverse event during PK period. Complete one column per one event and cross the appropriate box.

	Event observed	Event observed
Describe		
Onset time	DAY MONTH YEAR	DAY MONTH YEAR
End time	DAY MONTH YEAR	DAY MONTH YEAR
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Appearance	☐ Isolated ☐ Intermittent ☐ Continuous	☐ Isolated ☐ Intermittent ☐ Continuous
Serious**	☐ Yes ☐ No	☐ Yes ☐ No
Event causality	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug
Relation to the test drug	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible
Action taken (concerning study drug dose)	☐ None ☐ Dose interrupted/ ☐ Dose reduced restarted ☐ Dose increased ☐ Drug stopped	☐ None ☐ Dose interrupted/ ☐ Dose reduced restarted ☐ Decreased ☐ Drug stopped
Action taken (concerning therapeutic medication)	☐ Yes* ☐ No	☐ Yes* ☐ No
Outcome	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae

* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form.

** According to the protocol serious is defined as fatal, life-threatening, permanently or temporarily disabling, requires inpatient hospitalization or prolongation of hospitalization, or is associated with congenital abnormality, cancer or overdose (either intentional or accidental). For any adverse event treated as serious, contact study monitor and fill in "SERIOUS ADVERSE EVENT REPORT".

Investigator's Signature:

Neoral[®] capsules/Equoral capsulesStudy No.: 53/EQ/01/PK
CT I phase**STUDY PERIOD VISIT 6/DAY 28**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

4th PK - PHYSICAL EXAMINATION - 12 hr after dosing

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
Head	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS- 12 hr after dosing

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Arm used: ☐ right ☐ left

Time of the test

Hr

mm

Radial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg)Diastolic
(mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

STUDY PERIOD VISIT 6/DAY 28

Name of the study: A Pharmacokinetic Conversion Study of Equival (VAX-CR) and Neorale® In Stable Adult Renal Transplant Recipients (Study No. S3JEEQ011P4Q)

Subject Code	Subject Initials	Subject No:	Center No:

Day Month Year

4th PK CONCOMITANT MEDICATION / TREATMENT

Has the concomitant medication changed since the day 27? ☐ Yes ☐ No Please cross the appropriate box.

Cause	1 = study indication

1 = oral 5 = sexual 9 = others
2 = s.o. 6 = normal
3 = lrn. 7 = normal
4 = i.v. 8 = intruded

2 = consistent disease
3 = adverse event (specify in the form "Adverse Events")
5 = treatment of rejection
6 = others, specify in the form "Comments"

Indication/Diagnosis
Please, specify according to
international classification of diseases
(ICD)

[illegible]

Investigator's Signature: _____

Neoral[®] capsules/Equoral capsulesStudy No.: 59/EQ/01/PK
CT Phase**STUDY PERIOD VISIT 6/DAY 29**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 59/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
Head	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Time of the test

Hr

mm

Arm used: ☐ right ☐ leftRadial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg)Diastolic
(mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

STUDY PERIOD		VISIT 6/DAY 29	
Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neuraf [®] in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)			
Subject Code	 Subject Initials	 Subject No.	 Center No.
	Date	 Day	 Month Year
ADVERSE EVENTS			
Please record any observed adverse event since the day 28. Complete one column per one event and cross the appropriate box.			
	Event observed	Event observed	
Describe			
Onset time	 DAY MONTH YEAR	 DAY MONTH YEAR	
End time	 DAY MONTH YEAR	 DAY MONTH YEAR	
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	
Appearance	☐ Isolated ☐ Intermittent ☐ Continuous	☐ Isolated ☐ Intermittent ☐ Continuous	
Serious**	☐ Yes ☐ No	☐ Yes ☐ No	
Event causality	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	
Relation to the test drug	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	
Action taken (concerning study drug dose)	☐ None ☐ Dose interrupted/ restarted ☐ Dose reduced ☐ Drug stopped ☐ Dose increased	☐ None ☐ Dose interrupted/ restarted ☐ Dose reduced ☐ Drug stopped ☐ Dose increased	
Action taken (concerning therapeutic medication)	☐ Yes* ☐ No	☐ Yes* ☐ No	
Outcome	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	
* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form. ** According to the protocol serious is defined as fatal, life-threatening, permanently or temporarily disabling, requires inpatient hospitalization or prolongation of hospitalization, or is associated with congenital abnormality, cancer or overdose (either intentional or accidental). For any adverse event treated as serious, contact study monitor and fill in "SERIOUS ADVERSE EVENT REPORT".			
Investigator's Signature:			

STUDY PERIOD VISIT 6/DAY 29

Scope of the study: A Pharmacoeconomic Comparison Study of Equival (VAX-OR) and Neora® in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/RPQ)

Subject Code

Subject Mailed **Subject No:** **Center No:**

CONCOMITANT MEDICATION / TREATMENT

Has the concomitant medication changed since the day 28?

	Yes	No
1. Do you have a current driver's license?	☐	☐
2. Do you have a current vehicle registration?	☐	☐
3. Do you have a current insurance policy?	☐	☐
4. Do you have a current title?	☐	☐
5. Do you have a current sales tax certificate?	☐	☐
6. Do you have a current license plate?	☐	☐
7. Do you have a current title transfer fee?	☐	☐
8. Do you have a current title transfer tax?	☐	☐
9. Do you have a current title transfer fee and tax?	☐	☐
10. Do you have a current title transfer fee and tax and title transfer fee and tax?	☐	☐

If yes, please record on this form details of all changed medication since the day 28.

Cause	1 = study indication

Review

Applied Diagnosis

Please, specify according to

International classification of diseases

100

20000000

[illegible]

Total daily dose

Part 2

Case

Start Date

End Date

Comparing?

Yes No

Yes No

□

☐

□ □ □

□ □ □

1	2
3	4
5	6

1000

1111

77

11

LE

1001

[illegible]

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466

[illegible]

1

Investigator's Signature: _____

STUDY PERIOD

VISIT 7/ DAY 35

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK
CT I phase**STUDY PERIOD VISIT 7/DAY 35**

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

PHYSICAL EXAMINATION

Please perform a physical examination and cross the appropriate box.

	Not Examined	Normal	Abnormal	If abnormal, please specify
General appearance	☐	☐	☐	
Skin	☐	☐	☐	
lead	☐	☐	☐	
Eyes/Ears/Nose/Throat	☐	☐	☐	
Neck	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Breast (female)	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Neurological	☐	☐	☐	

VITAL SIGNS

Measurement of blood pressure and pulse after 5 minutes at rest in sitting position.

Please use the same arm for each measurement throughout the study!

Arm used: ☐ right ☐ left

Time of the test

Hr

mm

Radial pulse rate
(bpm)

Blood pressure

Systolic
(mmHg)/ Diastolic
(mmHg)

Body temperature

°C

Body weight:

Kg

Investigator's Signature: _____

STUDY PERIOD VISIT 7/DAY 35

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No. 53/EQ/01/PK)

Subject Code

Date

ADVERSE EVENTS

Please record any observed adverse event since the day 29. Complete one column per one event and cross the appropriate box.

	Event observed	Event observed
Describe		
Onset time	DAY MONTH YEAR	DAY MONTH YEAR
End time	DAY MONTH YEAR	DAY MONTH YEAR
Intensity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Appearance	☐ Isolated ☐ Intermittent ☐ Continuous	☐ Isolated ☐ Intermittent ☐ Continuous
Serious**	☐ Yes ☐ No	☐ Yes ☐ No
Event causality	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug	1 ☐ Study indication 5 ☐ Concomitant med. 2 ☐ Test drug 6 ☐ Coexistent disease 3 ☐ Low efficacy 7 ☐ Others 4 ☐ Withdrawal of the test drug
Relation to the test drug	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible	☐ Definite ☐ Not Assessable ☐ Probable ☐ None ☐ Possible
Action taken (concerning study drug dose)	☐ None ☐ Dose interrupted/ ☐ Dose reduced restarted ☐ Dose increased ☐ Drug stopped	☐ None ☐ Dose interrupted/ ☐ Dose reduced restarted ☐ Dose increased ☐ Drug stopped
Action taken (concerning therapeutic medication)	☐ Yes* ☐ No	☐ Yes* ☐ No
Outcome	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae	☐ Recovered ☐ Ongoing ☐ Recovered with sequelae

* Treatment given to alleviate any adverse event must be entered on the Concomitant Medication form.

* According to the protocol serious is defined as fatal, life-threatening, permanently or temporarily disabling, requires inpatient hospitalization or prolongation of hospitalization, or is associated with congenital abnormality, cancer or overdose (either intentional or accidental). For any adverse event treated as serious, contact study monitor and fill in "SERIOUS ADVERSE EVENT REPORT".

Investigator's Signature: _____

Neoral® capsules/Equoral capsules

Study No.:53/EQ/01/PK

CT 1, phase

CyA BTL AND DOSAGE - SUMMARY

Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral® in Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)

Subject Code Date
Subject Initials Subject No. Center No. Day Month Year

PRE-STUDY PERIOD

Visit/Day	Date and time	Current dose of Neoral capsules	CsA level	Next dose of Neoral capsules
Previous CyA BTL				
Previous CyA BTL				
Visit 1/Day -7				

STUDY PERIOD

Visit/Day	Date and time	Current dose of cyclosporine	CsA level	Next dose of cyclosporine (Neoral or /Equoral capsules)
Visit 2/Day 0				
Visit 3/Day 15				
Visit 4/Day 18				
Visit 5/Day 21				
Visit 6/Day 29				
Visit 7/Day 35				

Investigator's Signature:

Neoral[®] capsules/Equoral capsulesStudy No.: 53/EQ/01/PK
CT 1, phase**STUDY END VISIT 7/DAY 35**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

SUBJECT COMPLETION/WITHDRAWAL

Did the subject complete the study:

☐ Yes☐ No

If No, please complete the following:

Reason for withdrawal:

(Please cross the single most appropriate reason only)

- ☐ Adverse Event (Adverse Event must be completed)
- ☐ Serious Adverse Events (Adverse Event must be completed)
- ☐ Lack of tolerability
- ☐ Treatment failure
- ☐ Withdrawal of consent
- ☐ Protocol deviation
- ☐ Lost for follow-up (non-compliance)
- ☐ Pregnancy
- ☐ Termination by the sponsor
- ☐ Other, specify

Details:

Date and time of subject's withdrawal
Please record with appropriate precision:

DAY

MONTH

YEAR

hh

mm

Investigator's Signature: _____

Neoral[®] capsules/Equoral capsulesStudy No.: 53/EQ01/PK
CT Phase**STUDY END VISIT 7/DAY 35**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients (Study No.: 53/EQ01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

COMMENTS

Please, write legibly

Investigator's Signature: _____

Neoral[®] capsules/Equoral capsulesStudy No.:53/EQ/01/PK
CT I phase**STUDY END VISIT 7/DAY 35**Name of the study: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] In Stable Adult Renal Transplant Recipients (Study No.:53/EQ/01/PK)

Subject Code

Subject Initials

Subject No.

Center No.

Date

Day

Month

Year

INVESTIGATOR'S AND MONITOR'S STATEMENTS

I hereby certify that I have carefully examined all the data recorded in this Case Report Form for accuracy and completeness and I accept Full responsibility for all the data entered onto them.

Investigator:

Signature:

Date:

Monitor:

Signature:

Date:

Equoral® capsules

16. Appendices

16.1 Study Information

- 16.1.3** List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) – Representative Written Information for Patient and Sample Consent Form

Votes of IECs

Representative Written Information for Patient

INFORMATION FOR PATIENT

(1 original to be filed in a patient's CRF and 1 copy to be given to a patient)

Name of a doctor who informed a patient about the study:.....
 Study number: 53/EQ/01/PK
 Study title: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and
 Neoral® in Stable Adult Renal Transplant Recipients
 Sponsor: IVAX – CR, Ostravská 29, 747 70 Opava 9, Czech Republic

Dear Madam/Sir,

Your doctor has offered you your participation in the clinical research project which will evaluate the new generic cyclosporine product Equoral capsules. In the study the pharmacokinetic profile of Equoral capsules after the switch from Neoral® capsules will be evaluated in stable adult renal transplant patients. Besides, the safety and tolerability of the product will be evaluated.

The product Equoral capsules whose active ingredient is cyclosporine is used to prevent and treat rejection of transplant tissue and treat some autoimmune diseases induced by an excessive formation of antibodies against own body's cells and tissues.

Before you make a definitive decision if to accept your participation in the study or not we kindly ask you to carefully read the following information.

Study objective

The objective of the study is to evaluate the pharmacokinetic profile of the product Equoral capsules and the safety/tolerability parameters of the product.

Study duration

Pre-screening period will last 1 week. The participation of each patient in the study will last 5 weeks.

Number of enrolled patients

About 100 patients in 5 countries will be enrolled in the study.

Methods

You will be pre-screened into the study on the basis of selection criteria, physical examination and your suitability for enrollment to the study. Then you will obtain "Information for Patients". On the day -7, before the start of the study, you will be asked by the investigator to sign the Informed Consent and the samples for cyclosporine blood trough level, hematology, biochemistry and urinalysis will be collected. Those of you who fulfill the selection criteria will be enrolled into the study on the day 0 and on the same day the first (abbreviated – 2-hour) pharmacokinetic study will be performed. During this study 3 blood samples from you will be taken at

0, 1 and 2 hours. On the day 13 you will be admitted to the hospital and the second pharmacokinetic (12-hour) study will be performed. On the day 15 in the morning you will be switched from Neoral capsules to Equoral capsules at an equivalent dosage (milligrams: milligrams) and you will be discharged from the hospital. You will be asked to come for check-up on the day 18 and 21. On the day 21 the third pharmacokinetic (abbreviated – 2-hour) study will be performed. Then you will be asked to come on the day 27. On the day 27 in the afternoon you will be admitted again to the hospital and the forth (12-hour) pharmacokinetic study on the day 28 will be performed. From the morning on the day 29 you will be switched to Neoral capsules. You will be asked to come for the last check-up on the day 35.

In the course of the study you will visit the doctor according to the dates agreed (see Flow chart of the study at the end of this information sheet). 7 visits are scheduled in total. During each visit you will undergo clinical and physical examination. The adverse events, assessments of clinical symptoms and tolerability will be recorded. At screening and on the day 21 blood and urine samples will be collected. At the screening and on the days 18, and 35 blood samples for cyclosporine determination will be collected.

Monitoring of adverse drug reactions

Safety parameters will be monitored during the study, namely blood pressure, heart rate, radial pulse, body weight, laboratory results and the incidence of adverse reactions. The most frequently observed adverse drug reactions are increased growth of hair on the body or face, swollen gums, shakiness of the hands, renal dysfunction, and high blood pressure and liver problems. Less frequent adverse drug reactions are headaches, skin rash, increased weight, fluid retention, fatigue and weakness, feeling of heavy legs, anorexia, nausea, vomiting, sensations of heat in the hands and feet, loss of vision and in rare cases tumors. All your difficulties including those which do not seem to be related with the product administration will be monitored and recorded during the study.

Restrictions, limitations and premature discontinuation of the study

All other drugs can be used during the study only after your investigator's consent. The investigator can prematurely discontinue the administration of the test drug in the case of necessity to administer other drugs which may interfere with the test drug or affect the results of the clinical study, in the case of incidence of serious adverse reactions or if he/she finds out that a patient broke his/her study obligations.

Patient Diary

When entering the study you will receive so-called "Patient diary", in which you will record consumption of the products, concomitant administration of any other drugs and all difficulties which appear during the therapy.

Study monitoring

A representative of TransMed S.A.L. will monitor the course of the study. The study monitor will verify exactness of the information recorded in your Case Report Form by checking them with those in original medical record. You will be identified by a code during the study. The records according to which you can be identified and all

Nsoral[®] capsules/Equoral capsules

Study No.:53/EQ/01/PK

the data about the course and results of the study relating to you are confidential and will not be published. Besides the medical team doing the examinations, the data can only be revealed to qualified and authorized personnel of the State Authority, the Ministry of Health, or foreign health institution, Ethics Committee and personnel of pharmaceutical company IVAX-CR a.s. sponsoring the study. All the above mentioned institutions are obliged to keep the confidential information secret. Provided the study results will be published your name will not be disclosed.

Insurance, patient's rights and alternative therapy

In case of any damage due to your participation in this study, you will receive immediate appropriate medical treatment. Compensation of this treatment will be provided by Insurance company. Any damage will be classified and evaluated as damage if induced due to your participation in the clinical trial and directly related to the test medication. Insurance company will not pay compensation for the treatment of any other damage or disease - that means any other damage induced by any activity which is different from that implemented in the protocol of the study and instructions given by the investigator, damage as a result of any other treatment given, or a disease with no relationship to the test medication.

Participation in the study is absolutely voluntary. Provided you make the decision not to participate further in the study or decide to withdraw during the study, you can do so at anytime without even stating the reasons and your decision will not have any impact on the quality of the care provided. Provided you decide to discontinue the study please announce your decision to your nurse or investigator. Your participation in the study can be discontinued by the investigator or by IVAX-CR a.s., if they come to the conclusion that it is better for you. In such case we will inform you immediately.

During the study, great attention will be paid to securing patient's rights and to his/her voluntary decisions. The study must be approved by the Independent Ethics Committee judging especially patient's rights.

If any new information appears during the study which may influence your decision to continue with the study you will be informed immediately.

Provided you decide to participate in the study you will be asked to attend the examinations in the intervals stated above.

In this information material we have tried to summarize all the important information about the study. Provided anything is not clear to you or you want to know any further information please contact your Investigator or nurse. They will be glad to answer your questions.

Thank you for your time spending by reading this document.

Neoral® capsules/Equoral capsules

Study No.: 53/EQ/01/PK

Investigator

Nurse

Phone No.: Phone No.:

Addresses:

FLOW CHART OF THE VISITS AND PROCEDURES							
Screening period		Study period					
Visit	1.	2.	3.	4.	5.	6.	7.
Day	Day -7	Day 0	Day 13-15	Day 18	Day 21	Day 27-29	Day 35
General medical history	X						
Physical examination, Vital signs	X	X	X	X	X	X	X
Patient selection criteria	X						
Signed Informed consent	X						
Cyclosporine level determination	X			X			X
Blood samples	X	X	X	X	X	X	X
Urine samples	X					X	
Concomitant medication	X	X	X	X	X	X	X
Adverse events assessment		X	X	X	X	X	X
Abbreviated pharmacokinetics (at 0, 1, and 2 hours)		X			X		
12-hour pharmacokinetics			Hospitalization X			Hospitalization X	

Equoral[®] capsules

Sample Consent Form

INFORMED CONSENT*(1 original sheet to be filed in a patient's CRF and 1 copy to be given to a patient)*

First names and surname:.....
 Date of birth:.....
 Address:.....
 Patient's code:.....

Study number: 53/EQ/01/PK

Study title: A Pharmacokinetic Conversion Study of Equoral (IVAX-CR) and Neoral[®] in Stable Adult Renal Transplant Recipients

I hereby confirm that I was familiarized with the character, objective, range, significance and principles of the study on EQUORAL and NEORAL capsules by, the investigator. I was explained the method of conduct of the clinical research. All the information given to me by the investigator were fully comprehensible to me. I was given sufficient time to ask about details of the expected course of the study. I received the "Information for patient" and acknowledge that I will respect all the instructions written there.

I oblige myself to fulfil the obligations arising from my participation in the study, namely:

- use all drugs only after the investigator's previous consent
- inform the investigator about all difficulties which may occur in a course of the study
- adhere to all investigator's instructions given to me before, during and after the study

I was informed of the incidence of adverse reactions which may occur and pledge myself to immediately report all my subjective difficulties which I may experience during the study to the investigator.

I agree with making the study documentation available to the State Authorities, Ethics Committee and responsible Sponsor's personnel without any breach of confidential information. I understand that they control the documentation on a basis of directives of the European Union with objective to secure quality and precision of the data obtained.

I also agree with publishing the study results provided my identification would not be disclosed.

I was also informed that an insurance agreement was signed covering any damage of my health which might occur after administration of the drug which is subject to the study. I was also familiarized with my obligations connected with the insurance, especially to immediately report the investigator any change of my health conditions.

I was informed that if I agree with my participation in the study I would be compensated for my travelling expenses and loss of profit.

I hereby declare that my participation in the study is absolutely voluntary. I was informed that I can withdraw this Informed Consent at any time without even stating the reason for doing so and my decision will not anyhow affect by future therapy provided. However, I will report the investigator my intention to discontinue the study in time.

Neoral[®] capsules/Equoral capsules

Study No.: 53/EQ/01/PK

I received a copy of "Information for patient" and a copy of signed "Informed Consent".

.....
Patient's signature

.....
Investigator's signature

.....
Place, date
(please fill in by hand)

.....
Place and date
(please fill in by hand)

Addresses:

.....
.....

Equoral[®] capsules

16. Appendices

16.1 Study Information

16.1.4 List and Description of Investigators and Other Important Participants in the Study, including brief (1 page) CVs or equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study

Curricula Vitae Investigators

Curricula Vitae Statisticians

Equoral® capsules

16. Appendices

16.1 Study Information

16.1.5 Signature of Principal of Co-ordinating Investigator(s) or Sponsor's Responsible Medical Officer Depending on the Regulatory Authority's Requirement

Sponsor's Responsible Medical Officer Signature

Study Title: A Pharmacokinetic Conversion Study of Equoral® (IVAX-CR) and Neuronal in Stable Renal Transplant Recipients

Study Author: Eva Kopečná, MD

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and the results of the study.

Sponsor's Responsible Medical Officer: Assoc. prof. Vojtěch Kamarád, MD, DrSc

Signature

Affiliation: IVAX Pharmaceuticals s.r.o.
Ostravské 29
747 70 Opava – Komárov
Czech Republic

Date: _____

16. Appendices**16.1 Study Information****16.1.6 Listing of Patients receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used**

Equoral[®] capsules

16.1.6 Listing of Patients Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used

Not applicable

16. Appendices

16.1 Study Information

16.1.7 Randomisation Scheme and Codes (Patient Identification and Treatment assigned)

16.1.7 Randomisation Scheme and Codes (Patient Identification and Treatment assigned)

Not applicable

16. Appendices

16.1 Study information

16.1.8 Audit Certificates (if available)

Equoral[®] capsules

16.1.8 Audit Certificates

Not applicable

16. Appendices

16.1 Study Information

16.1.9 Documentation of Statistical Methods

16. Appendices

16.1 Study Information

16.1.9 Documentation of Inter-laboratory Standardisation Methods and Quality Assurance Procedures if used

16.1.10 Documentation of Inter-laboratory Standardisation Methods and Quality Assurance Procedures if used

Not applicable

Equoral® capsules

GLP Certificates Local Laboratories

16. Appendices**16.1 Study Information****16.1.11 Publication Based on the Study**

Publication Based on the Study



The Pharmacokinetics of Equoral Versus Neoral in Stable Renal Transplant Patients: A Multinational Multicenter Study

M.A. Masri, M. Haberal, A. Rizvi, A. Stephan, N. Bilgin, A. Naqvi, A. Barbari, G. Kamel, N. Zafar, R. Emiroglu, T. Çolak, K. Manzoor, V. Matha, V. Kamarad, S. Rizk, A.R. Itany, and I. Shehadeh

ABSTRACT

We studied the pharmacokinetics (PKs) of the new generic cyclosporine formulation, Equoral capsules, after the switch from original formulation Neoral capsules in stable renal transplant patients. The study was carried out in accordance with the basic principles defined in the US 21 CFR Part 312.20 and the principles of the Declaration of Helsinki. The study included clinically stable first renal transplant patients maintained on cyclosporine with no rejection episode during the past 6 months. Hematology, biochemistry, and urine chemistry were determined on day 7, and day 21. The patients were all switched to Neoral (lot number 416MFD0601) on day 0 when the first sparse sampling PK was performed. On day 14 a 12-hour PK profile included predose, 30 minutes; 1 hour; 1 hour 30 minutes; 2 hours; 3 hours; 4 hours; 5 hours; 6 hours; 8 hours; 10 hours and 12-hour samples. Cyclosporine levels were determined using a CYA kit (Abbott TDx). On day 15 the patients were switched from Neoral capsules to Equoral capsules (lot ST111014) at an equivalent dosage (mg/mg). The second sparse sampling PK was performed on day 21 and a 12-hour PK was performed on day 28. On the morning of day 29 patients were switched from Equoral capsules to Neoral capsules at an equivalent dosage (mg/mg). Additional concentrations were measured on days -7, 18, and 35. Safety parameters were monitored at each visit. The pharmacokinetics of both formulations were equivalent. The mean AUC for Neoral and Equoral was 2856 and 2892, respectively. The ratios of *LSM* and the 90% confidence intervals for the *ln*-transformed parameters (AUC *0-t*, AUC *inf*, and *Cmax*) of Equoral and Neoral SGC were 98% and 95%, respectively, suggesting that Equoral and Neoral SGC are bioequivalent.

SINCE THEIR INTRODUCTION into transplantation, cyclosporine generic formulations have produced significant cost reduction. The results from many studies indicate similar graft and patient survival rates¹⁻⁷ under treatment with generics versus brand name products.

The US Food and Drug Administration (FDA) regulations stipulate that generics be tested in healthy volunteers in a four-way crossover study.⁸ Such studies are important to compare the bioavailability of the generic to the brand name; however, the drug is really intended to be used in a nonhealthy environment, ("the patient"). We studied the pharmacokinetics of a new generic cyclosporine formulation, Equoral capsules after the switch from the original formulation Neoral capsules in stable renal transplant patients.

MATERIALS AND METHODS

Equoral is a patented macrogel formulation developed by IVAX-Pharmaceuticals.⁹ The primary objective of the study was to compare the pharmacokinetics of the new generic cyclosporine formulation, Equoral capsules, after the switch from original formulation Neoral capsules. The secondary objective of the study was to evaluate C₁, C₂, B₁L, and changes in CyA dosage. The study was performed by the CRO Trans Med s.a.l. (Beirut Lebanon) in accordance with the basic principles defined in the US

Gaskert University Ankara Turkey, SIUT Karachi Pakistan Rizk Hospital, Beirut, Lebanon and University of Prague and IVAX-CR CZ Republic, Prague, Czech Republic.

Address reprint requests to Marwan A. Masri, MD, Rizk Hospital, PO Box 11-3268, Beirut, Lebanon. E-mail: Marwan.Masri@Mayaonline.com

Table 1. Twelve-Hour Pharmacokinetics of Neoral and Equoral

	PK mean concentration profiles											
	T0	T30	T1	T1:30	T2	T3	T4	T5	T6	T8	T10	T12
Neoral	131	188	589	705	693	473	348	289	220	169	132	116
Equoral	140	220	514	659	670	481	356	278	225	168	135	123

21 CFR Part 312.20, the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, Somerset West, 1996) and the ICH harmonized tripartite guidelines regarding good clinical practices. The protocol was also approved by the ethics committee in each center and/or the national ethics committee in each country.

The inclusion criteria were first renal transplants with no rejection episode during the previous 6 months who were clinically stable with acceptable safety/tolerance to Neoral capsules; three last whole blood trough cyclosporine levels in the range of 70 to 200 ng/mL (specific) with stable serum creatinine values in the past 3 months with no trend to increase; no hepatic dysfunction during the past 6 months (increase of aminotransferase <100% above the limit) or history of alcohol or drug abuse or signs of alcohol-induced organ damage and no clinical symptoms of CMV infection in the past 6 months; no history or evidence of malignancy or any significant infection; blood pressure in normotensive range with or without antihypertensive medication. The patients were all maintained on cyclosporine in double or triple combination with prednisone, azathioprine, mycophenolate mofetil (doses of cyclosporine as 8 mg/kg/d). This dose had to be stable over the previous 14 days prior to entry. Doses of concomitant medications had to be stable for 14 days prior to study entry. In addition the subject had to have the ability to communicate with the investigator and to provide written informed consent.

Exclusion criteria included a significant history of hypersensitivity to cyclosporine or related products, such as castor oil, olive oil,

or corn oil; pregnancy or lactating females; premenopausal woman of childbearing potential not using safe contraception; more than one renal transplant or grafts of other organs (eg, pancreas); use of routine immunosuppressive therapy other than azathioprine, mycophenolate mofetil, or prednisone; uncontrolled blood pressure (resistant to antihypertensive therapy and despite reduction of cyclosporine dose); history of chronic alcoholism, drug or narcotic abuse; history of myocardial infarction within 6 months of enrollment or uncontrolled cardiac arrhythmia and clinically relevant disease (including nervous system); or other abnormal condition that may compromise function of gastrointestinal tract, kidney, or liver or might influence cyclosporine pharmacokinetics; exposure to any drug interfering with cyclosporine pharmacokinetics or potentially nephrotoxic drug within 14 days prior to study entry.

In accordance with the Declaration of Helsinki, subjects had the right to withdraw from the study at any time for any reason. The principal investigator had the right to withdraw subjects from the study in case of serious adverse events, the necessity to prescribe any excluded medication, protocol violations, withdrawal of consent, failure to return for scheduled visit or other reason. The subjects may also be withdrawn if necessary to protect their health and the integrity of the study. In case of a questionable situation the Clinical Trial Monitor or the Medical Contact was consulted. Continued participation of any patient who violated the protocol was decided by the Sponsor's Medical Contact. Patients who were not evaluable due to protocol violations that were within the control of the investigator were not considered as completed

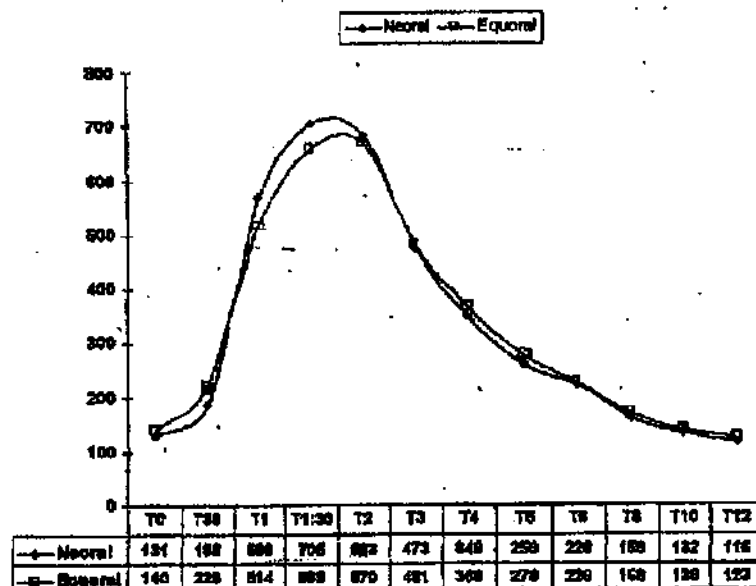


Fig 1. Twelve-hour pharmacokinetic profiles of Equoral versus Neoral.

Table 2. Comparison of the T₀, T₁, T₂ of Equoral and Neoral at Three Different Occasions

	Neoral			Equoral		
	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂
Average	109.8	616.5	680.5	109.3	558.5	580
SD	14.41	23.50	0.50	17.28	15.5	6.00
CV	13.13	3.81	0.07	15.80	2.78	0.87

subjects. Subjects who did not complete the study were not replaced. Subjects who withdrew due to adverse events were classified as "censored" and not replaced. Should a patient have decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the patient withdrawal was performed with an explanation of why the subject withdrew from the study. Each subject's withdrawal was recorded in a CRF.

Study Design

On day -7 and day 21 hematology, biochemistry, and urinalysis were determined as well as the first sparse sampling PK on Neoral (lot no. 416MFD0601, expiry date 06/2004) on day 0. On day 14 the 12-hour PK included predose, 30 minutes; 1 hour; 1 hour 30 minutes; 2 hours; 3 hours; 4 hours; 5 hours; 6 hours; 8 hours; 10 hours and 12 hours samples. The 12 cyclosporine levels were determined using the same CYA kit (lot no. 85619Q100, batch no. 9797-60, expiry 20/2/2004, calibrators lot no. 88724Q100, control lot no. 77414Q100, Abbott TDX). On day 15 the patients were switched from Neoral capsules to Equoral capsules (lot 5T111014, expiry 11/2003) at an equivalent dosage (mg/mg). The second sparse sampling PK was performed on the day 21 with a 12-hour PK performed on day 28. On day 29 in the morning the patients were switched from Equoral capsules to Neoral capsules at an equivalent dosage (mg/mg). Additional BTL were measured on days -7, 18, and 35. Safety parameters were monitored at each visit. The dose of cyclosporine was not adjusted throughout the study.

RESULTS

The pharmacokinetics of both formulations were equivalent at all times during the 12-hour period (Table 1; Fig 1).

Seventy percent of the patients displayed a C_{max} at 1:30 minutes, 20% at T₁, and only 10% at T₂. The C_{max} in all centers was far lower than those reported from European or US patients. The mean AUC for Neoral and Equoral was 2856 and 2892, respectively. The C_{max} for Equoral was 743 ng/mL and for Neoral 773 ng/mL, respectively. There were no significant changes in the creatinine levels for both Equoral at 1.24 mg/dL and Neoral at 1.23 mg/dL. There were no serious adverse effects during the study; none of the patients withdrew from the study. The stability of the pharmacokinetics was also similar as determined by the CV of three consecutive measurements performed 7 days apart (Table 2).

Both formulations had similar T₂ (C₂) for the two measurements performed on day 7 and day 14 for Neoral and day 21 and day 28 for Equoral (Fig 2).

The ratios of LSM and the 90% confidence intervals for the in-transformed parameters (AUC 0-t, AUC inf, and C_{max}) of Equoral and Neoral SGC were 98% and 95%, respectively, which were within the 80% to 125% FDA acceptance range. These results indicate that Equoral and Neoral SGC are bioequivalent.

REFERENCES

- Stephan AG, Barbari A, Masri MA, et al: Evaluation of the new cyclosporine formulation, Concsupren, in renal transplant patients. *Transplant Proc* 28:1348, 1996
- Masri MA, Barbari A, Stephan A, et al: Cyclosporine pharmacokinetics in stable renal transplant patients: effect of formulation Sandimmune versus Concsupren versus Neoral. *Transplant Proc* 28:1318, 1996
- Kamel G, Stephan A, Masri MA, et al: Donor-specific transfusion under the new cyclosporine A formulation Concsupren versus azathioprine, Imuran. *Transplant Proc* 29:2960, 1997
- Stephan A, Masri MA, Barbari A, et al: A one-year comparative study of Neoral vs Concsupren in de novo renal transplant patients. *Transplant Proc* 30:3533, 1998
- Barbari A, Stephan A, Kamel G, et al: Experience with new cyclosporine formulations: Concsupren and Neoral in renal transplant patients. *Transplant Proc* 29:2941, 1997
- Masri MA, Barbari A, Stephan A, et al: Safe and cost effective

Neoral Vs Equoral (T₀, T₁, T₂)

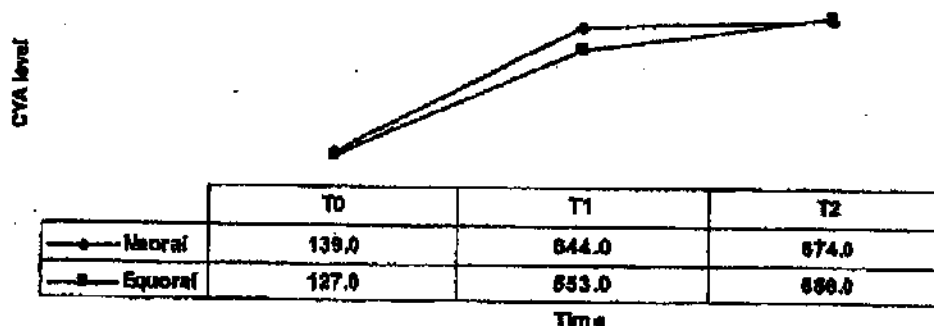


Fig 2. T₀, T₁, T₂ of Neoral versus Equoral at two different time intervals: day 7 and day 14 for Neoral and day 21 and day 28 for Equoral.

PHARMACOKINETICS OF EQUORAL VERSUS NEORAL

83

conversion from Neoral to Conspren soft gelatin capsules in stable renal transplant patients: a 1-year study. *Transplant Proc* 31:3302, 1999

7. Masri MA, Stephan A, Barbari A, et al: Cyclosporine formulations: is there really a difference? *Transplant Proc* 32:1468, 2000

8. Masri MA: The generics in transplantation and rules on their use. *Experimental and Clinical Transplantation* 1:65, 2003

9. Andrysek T, Masri M, Jegorov A, et al: Equoral, new cyclosporine drug delivery system, versus neoral: a bioequivalence study in healthy volunteers. *Transplant Proc* 35:203, 2003

Equoral[®] capsules

16. Appendices

16.1 Study Information

16.1.11 Important Publications Referenced in the Report

Equoral® capsules

16.1.12 Important Publications Referenced in the Report

Not applicable

16. Appendices**16.2 Patient Data Listings****16.2.1 Discontinued Patients**

Equoral[®] capsules

16.2.1 Discontinued Patients

Not applicable

16. Appendices

16.2 Patients Data Listings

16.2.2 Protocol Deviations

16.2.2 PROTOCOL DEVIATIONS

PROTOCOL DEVIATIONS

Phase I (N = 48)

<u>Patient</u>	<u>Sex</u>	<u>Age</u>	<u>Reason(s)</u>
1/1	M	46	Inclusion criteria: hypertension on day -7
3/1	M	36	Inclusion criteria: hypertension on day -7 low trough level on day -7
4/1	M	67	Inclusion criteria: hypertension on day -7 low trough level on day -7
5/1	M	59	Inclusion criteria: low trough level on day -7
6/1	M	45	Inclusion criteria: low trough level on day -7
8/1	M	33	Inclusion criteria: low trough level on day -7
10/1	Z	37	Inclusion criteria: hypertension on day -7
11/1	M	29	Inclusion criteria: hypertension on day -7 low trough level on day -7
13/1	M	30	Inclusion criteria: low trough level on day -7
15/1	M	54	Inclusion criteria: hypertension on day -7 low trough level on day -7
16/1	Z	41	Inclusion criteria: low trough level on day -7

Equoral[®] capsules

17/1	M	39	Inclusion criteria: hypertension on day -7
18/1	M	45	Inclusion criteria: hypertension on day -7
19/1	M	30	Inclusion criteria: hypertension on day -7
21/1	Ž	36	Inclusion criteria: high trough level on day -7
22/1	M	27	Inclusion criteria: hypertension on day -7
23/1	M	35	Inclusion criteria: hypertension on day -7
24/1	Ž	37	Inclusion criteria: hypertension on day -7
25/1	M	31	Inclusion criteria: hypertension on day -7
27/1	M	41	Inclusion criteria: hypertension on day -7
29/1	M	28	Inclusion criteria: low trough level on day -7
30/1	M	38	Inclusion criteria: hypertension on day -7
2/3	Ž	32	Inclusion criteria: hypertension on day -7)
4/3	M	33	Inclusion criteria: high trough level on day -7
5/3	M	32	Inclusion criteria: hypertension on day -7
8/3	M	32	Inclusion criteria: hypertension on day -7
9/3	M	31	Inclusion criteria: hypertension on day -7

10/3	M	27	Inclusion criteria: high trough level on day -7
2/4	M	25	Inclusion criteria: high trough level on day -7
3/4	M	28	Inclusion criteria: hypertension on day -7
4/4	Ž	28	Inclusion criteria: high trough level on day -7
5/4	M	18	Inclusion criteria: high trough level on day -7
6/4	M	48	Inclusion criteria: high trough level on day -7
7/4	M	31	Inclusion criteria: high trough level on day -7
8/4	M	31	Inclusion criteria: significantly increased ALAT on day -7 high trough level on day -7
9/4	M	26	Inclusion criteria: high trough level on day -7
10/4	M	38	Inclusion criteria: hypertension on day -7
11/4	M	29	Inclusion criteria: hypertension on day -7
13/4	M	26	Inclusion criteria: hypertension on day -7
14/4	Ž	49	Inclusion criteria: low trough level on day -7
15/4	Ž	26	Inclusion criteria: significantly increased ALAT and ASAT on day -7)
16/4	M	50	Inclusion criteria: hypertension on day -7

Equoral® capsules

1/5	M	25	Inclusion criteria: high trough level on day -7
3/5	Ž	37	Inclusion criteria: hypertension on day -7
5/5	Ž	25	Inclusion criteria: high trough level on day -7
6/5	M	28	Inclusion criteria: hypertension on day -7
7/5	M	23	Inclusion criteria: hypertension on Day -7
8/5	M	29	Inclusion criteria: high trough level on day -7

Equoral[®] capsules

16. Appendices

16.2 Patient Data Listings

16.2.3 Patients Excluded from Pharmacokinetic Analysis

16.2.3 Patients Excluded from Pharmacokinetic Analysis

Not applicable

Equoral[®] capsules

16. Appendices

16.2 Patient Data Listings

16.2.4 Demographic Data

Equoral® capsules

16. Appendices

16.2 Patient Data Listings

16.2.5 Compliance and/or Drug Concentration Data (if available)

Center No. 1 (Rizk Hospital, Beirut, Lebanon)

S.No.	C.No.	Subject	Day	Drug	Dose	Trough level	30 min.	1 hr	1/30h	2 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h
Subject No. 1 - Rizk Hospital, Lebanon																	
1	1	MAB	-7	Neoral	150	157	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	138	-	978	-	653	-	-	-	-	-	-	-
			14	" (AUC)	150	135	266	998	967	759	457	328	255	236	188	168	169
			18	Equoral	150	148	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	172	-	517	-	1009	-	-	-	-	-	-	-
			28	" (AUC)	150	131	143	366	632	618	416	286	240	186	142	132	107
			35	Neoral	150	98	-	-	-	-	-	-	-	-	-	-	-
2	1	HKY	-7	Neoral	150	168	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	142	-	967	-	893	-	-	-	-	-	-	-
			14	" (AUC)	150	132	251	721	958	787	378	113	232	195	96	122	149
			18	Equoral	150	179	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	138	-	1028	-	796	-	-	-	-	-	-	-
			28	" (AUC)	150	149	326	960	948	716	452	361	241	219	167	153	120
			35	Neoral	150	174	-	-	-	-	-	-	-	-	-	-	-
3	1	PFM	-7	Neoral	125	43	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	125	43	-	185	-	194	-	-	-	-	-	-	-
			14	" (AUC)	125	34	46	133	255	283	183	332	88	70	25	35	32
			18	Equoral	125	32	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	125	28	-	49	-	166	-	-	-	-	-	-	-
			28	" (AUC)	125	31	30	214	263	242	182	100	71	60	45	36	22
			35	Neoral	125	31	-	-	-	-	-	-	-	-	-	-	-
4	1	KBA	-7	Neoral	150	89	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	64	-	727	-	361	-	-	-	-	-	-	-
			14	" (AUC)	150	31	48	525	557	355	178	100	84	66	66	48	48
			18	Equoral	150	46	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	44	-	283	-	520	-	-	-	-	-	-	-
			28	" (AUC)	150	46	85	437	457	341	138	93	73	51	60	54	39
			35	Neoral	150	49	-	-	-	-	-	-	-	-	-	-	-
5	1	GJW	-7	Neoral	125	40	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	125	48	-	890	-	390	-	-	-	-	-	-	-
			14	" (AUC)	125	39	46	354	608	534	194	119	112	79	52	48	41
			18	Equoral	125	37	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	125	34	-	483	-	410	-	-	-	-	-	-	-
			28	" (AUC)	125	28	236	560	507	352	200	120	99	82	55	49	48
			35	Neoral	125	34	-	-	-	-	-	-	-	-	-	-	-
6	1	GCB	-7	Neoral	50	21	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	50	20	-	178	-	168	-	-	-	-	-	-	-
			14	" (AUC)	50	10	215	239	149	96	87	36	35	22	8	16	11
			18	Equoral	50	26	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	50	13	-	250	-	136	-	-	-	-	-	-	-
			28	" (AUC)	50	19	20	181	210	172	83	60	45	30	28	23	23
			35	Neoral	50	12	-	-	-	-	-	-	-	-	-	-	-
7	1	SMA	-7	Neoral	100	98	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	92	-	779	-	423	-	-	-	-	-	-	-
			14	" (AUC)	100	66	235	803	357	398	173	149	135	105	87	65	80

			18	Equal	100	90	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	95	-	958	-	513	-	-	-	-	-	-	-
			28	" (AUC)	100	96	459	761	609	423	257	183	154	128	112	100	97
			35	Neural	100	90	-	-	-	-	-	-	-	-	-	-	-
8	1	SEM	-7	Neural	100	23	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	36	-	568	-	176	-	-	-	-	-	-	-
			14	" (AUC)	100	18	34	296	300	198	98	65	42	37	24	28	21
			18	Equal	100	23	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	24	-	342	-	166	-	-	-	-	-	-	-
			28	" (AUC)	100	24	29	104	356	277	145	80	74	52	33	30	16
			35	Neural	100	37	-	-	-	-	-	-	-	-	-	-	-
9	1	FAS	-7	Neural	225	89	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	225	113	-	1147	-	819	-	-	-	-	-	-	-
			14	" (AUC)	225	76	89	409	687	608	352	339	279	125	187	122	85
			18	Equal	225	98	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	225	87	-	1203	-	982	-	-	-	-	-	-	-
			28	" (AUC)	225	81	74	89	694	1241	559	360	319	207	175	116	98
			35	Neural	225	131	-	-	-	-	-	-	-	-	-	-	-
10	1	RAJ	-7	Neural	150	63	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	66	-	566	-	679	-	-	-	-	-	-	-
			14	" (AUC)	150	60	35	241	683	751	340	181	147	107	76	54	50
			18	Equal	150	69	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	58	-	287	-	641	-	-	-	-	-	-	-
			28	" (AUC)	150	84	107	398	830	751	387	232	179	156	87	75	70
			35	Neural	150	87	-	-	-	-	-	-	-	-	-	-	-
11	1	SSV	-7	Neural	100	31	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	34	-	100	-	323	-	-	-	-	-	-	-
			14	" (AUC)	100	28	24	127	401	371	149	81	61	61	39	16	25
			18	Equal	100	27	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	26	-	147	-	288	-	-	-	-	-	-	-
			28	" (AUC)	100	32	33	166	460	337	148	94	73	59	44	29	28
			35	Neural	100	36	-	-	-	-	-	-	-	-	-	-	-
12	1	SJS	-7	Neural	150	166	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	163	-	827	-	834	-	-	-	-	-	-	-
			14	" (AUC)	150	163	167	594	1050	842	521	380	296	253	215	136	154
			18	Equal	150	187	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	189	-	820	-	975	-	-	-	-	-	-	-
			28	" (AUC)	150	144	151	153	346	693	525	384	289	274	194	159	155
			35	Neural	150	170	-	-	-	-	-	-	-	-	-	-	-
13	1	AAZ	-7	Neural	150	53	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	50	-	199	-	641	-	-	-	-	-	-	-
			14	" (AUC)	150	44	92	605	696	468	221	161	145	108	72	60	57
			18	Equal	150	48	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	53	-	636	-	382	-	-	-	-	-	-	-
			28	" (AUC)	150	47	71	443	682	634	294	167	131	106	79	61	54
			35	Neural	150	65	-	-	-	-	-	-	-	-	-	-	-
14	1	NAN	-7	Neural	200	146	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	161	-	658	-	686	-	-	-	-	-	-	-
			14	" (AUC)	200	157	189	633	1231	995	565	369	282	239	183	187	141

			18	Equal	200	147	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	129	-	1185	-	772	-	-	-	-	-	-	-
			28	" (AUC)	200	167	326	606	972	999	478	389	278	222	174	160	150
			35	Neural	200	178	-	-	-	-	-	-	-	-	-	-	-
15	1	FEJ	-7	Neural	50	10	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	50	21	-	194	-	122	-	-	-	-	-	-	-
			14	" (AUC)	50	5	41	208	171	113	64	42	27	30	20	7	14
			18	Equal	50	15	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	50	13	-	71	-	116	-	-	-	-	-	-	-
			28	" (AUC)	50	13	15	120	183	147	72	37	32	27	20	22	22
			35	Neural	50	15	-	-	-	-	-	-	-	-	-	-	-
16	1	ZRC	-7	Neural	125	43	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	125	43	-	209	-	693	-	-	-	-	-	-	-
			14	" (AUC)	125	47	52	416	482	466	180	133	102	94	65	51	61
			18	Equal	125	88	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	125	59	-	273	-	789	-	-	-	-	-	-	-
			28	" (AUC)	125	46	44	144	472	593	298	160	112	96	73	75	37
			35	Neural	125	44	-	-	-	-	-	-	-	-	-	-	-
17	1	YNR	-7	Neural	150	85	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	97	-	687	-	590	-	-	-	-	-	-	-
			14	" (AUC)	150	73	225	808	916	665	374	262	205	169	118	99	89
			18	Follow-up	150	187	-	-	-	-	-	-	-	-	-	-	-
			21	Equal	150	82	-	394	-	703	-	-	-	-	-	-	-
			28	" (AUC)	150	78	164	566	703	702	427	269	190	159	109	84	61
			35	Neural	150	99	-	-	-	-	-	-	-	-	-	-	-
18	1	GAM	-7	Neural	100	91	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	87	-	610	-	583	-	-	-	-	-	-	-
			14	" (AUC)	100	83	210	635	709	599	390	242	200	184	112	108	93
			18	Equal	100	100	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	99	-	600	-	562	-	-	-	-	-	-	-
			28	" (AUC)	100	91	200	688	792	621	393	275	210	162	126	96	83
			35	Neural	100	83	-	-	-	-	-	-	-	-	-	-	-
19	1	AHB	-7	Neural	250	124	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	130	-	769	-	702	-	-	-	-	-	-	-
			14	" (AUC)	250	124	168	781	899	723	451	365	254	223	161	120	109
			18	Equal	250	133	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	137	-	788	-	766	-	-	-	-	-	-	-
			28	" (AUC)	250	141	178	729	874	781	438	381	266	248	172	141	135
			35	Neural	250	130	-	-	-	-	-	-	-	-	-	-	-
20	1	AMH	-7	Neural	250	147	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	133	-	751	-	745	-	-	-	-	-	-	-
			14	" (AUC)	250	133	210	890	789	715	466	418	322	276	200	218	154
			18	Equal	250	139	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	143	-	787	-	805	-	-	-	-	-	-	-
			28	" (AUC)	250	128	231	816	899	792	493	433	373	257	261	183	144
			35	Neural	250	118	-	-	-	-	-	-	-	-	-	-	-
21	1	MZH	-7	Neural	200	291	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	242	-	913	-	799	-	-	-	-	-	-	-
			14	" (AUC)	200	237	282	936	1073	830	689	573	447	391	319	290	266

			18	Equal	200	201	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	228	-	853	-	931	-	-	-	-	-	-	-
			28	" (AUC)	200	249	308	940	1105	879	625	580	472	399	302	287	280
			35	Neural	200	221	-	-	-	-	-	-	-	-	-	-	-
22	1	AMK	-7	Neural	200	133	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	143	-	733	-	696	-	-	-	-	-	-	-
			14	(AUC)	200	159	265	713	769	702	532	511	458	434	279	223	176
			18	Equal	200	151	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	138	-	719	-	733	-	-	-	-	-	-	-
			28	(AUC)	200	161	271	717	716	722	567	544	421	432	298	245	149
			35	Neural	200	135	-	-	-	-	-	-	-	-	-	-	-
23	1	AMC	-7	Neural	150	119	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	107	-	698	-	502	-	-	-	-	-	-	-
			14	(AUC)	150	110	217	697	711	553	459	346	321	278	197	134	101
			18	Equal	150	108	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	118	-	672	-	560	-	-	-	-	-	-	-
			28	(AUC)	150	117	232	639	693	514	478	400	319	284	205	159	98
			35	Neural	150	119	-	-	-	-	-	-	-	-	-	-	-
24	1	MAR	-7	Neural	300	151	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	300	140	-	558	-	922	-	-	-	-	-	-	-
			14	(AUC)	300	145	300	578	1000	931	485	402	400	310	203	156	152
			18	Equal	300	162	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	300	156	-	579	-	1013	-	-	-	-	-	-	-
			28	(AUC)	300	139	302	566	968	944	480	390	364	298	219	165	140
			35	Neural	300	151	-	-	-	-	-	-	-	-	-	-	-
25	1	HBM	-7	Neural	300	189	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	300	174	-	580	-	845	-	-	-	-	-	-	-
			14	(AUC)	300	177	221	945	990	834	731	402	400	351	243	189	190
			18	Equal	300	196	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	300	191	-	942	-	901	-	-	-	-	-	-	-
			28	(AUC)	300	156	219	987	1120	982	789	542	410	321	213	141	160
			35	Neural	300	205	-	-	-	-	-	-	-	-	-	-	-
26	1	RMC	-7	Neural	250	125	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	117	-	735	-	572	-	-	-	-	-	-	-
			14	(AUC)	250	120	212	700	710	880	847	429	312	260	187	132	140
			18	Equal	250	136	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	125	-	756	-	582	-	-	-	-	-	-	-
			28	(AUC)	250	135	160	670	770	760	509	431	377	290	201	187	151
			35	Neural	250	107	-	-	-	-	-	-	-	-	-	-	-
27	1	NCJ	-7	Neural	150	77	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	71	-	615	-	543	-	-	-	-	-	-	-
			14	(AUC)	150	71	107	630	640	555	399	354	301	239	146	89	85
			18	Equal	150	89	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	69	-	631	-	573	-	-	-	-	-	-	-
			28	(AUC)	150	66	190	693	701	612	411	384	315	207	145	103	67
			35	Neural	150	79	-	-	-	-	-	-	-	-	-	-	-
28	1	KEN	-7	Neural	100	93	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	106	-	356	-	796	-	-	-	-	-	-	-
			14	(AUC)	100	106	176	356	413	795	450	364	286	246	156	142	113
			18	Equal	100	91	-	-	-	-	-	-	-	-	-	-	-

			21	Follow-up	100	109	-	736	-	582	-	-	-	-	-	-
			28	(AUC)	100	103	199	341	449	834	503	373	240	173	137	99
			35	Neural	100	62	-	-	-	-	-	-	-	-	-	-
29	1	ZAM	-7	Neural	150	41	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	48	-	465	-	526	-	-	-	-	-	-
			14	(AUC)	150	48	243	465	513	826	439	300	210	153	89	42
			18	Equal	150	53	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	64	-	506	-	512	-	-	-	-	-	-
			28	(AUC)	150	66	271	672	579	899	375	249	153	148	69	37
			35	Neural	150	42	-	-	-	-	-	-	-	-	-	-
30	1	AKD	-7	Neural	200	70	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	76	-	966	-	713	-	-	-	-	-	-
			14	(AUC)	200	76	148	966	854	713	218	194	158	101	64	77
			18	Equal	200	83	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	92	-	1124	-	742	-	-	-	-	-	-
			28	(AUC)	200	49	129	906	1109	644	351	179	141	117	79	52
			35	Neural	200	70	-	-	-	-	-	-	-	-	-	-

Center No. 3 (Ankara, Turkey)

S.No.	C.No.	Name/Id	Day	Drug	Dose	Trough level	30-min	1hr	1/30h	2h	3h	4h	5h	6h	8h	10h	12h
1	3	H-D	-7	Neoral	200	168	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	118	-	696	-	722	-	-	-	-	-	-	-
			14	' (AUC)	200	147.2	133.8	220.6	830.4	625.1	693.2	427.7	276.8	240.7	167.7	144.3	132.6
			18	Equoral	200	168	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	111	-	736.8	-	866.6	-	-	-	-	-	-	-
			28	' (AUC)	200	146.9	242.1	551.6	627.7	790.7	690.7	377.8	287.9	209.2	132.4	152.3	179.7
			35	Neoral	200	174	-	-	-	-	-	-	-	-	-	-	-
2	3	D-E	-7	Neoral	250	177	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	175.2	-	584.9	-	491.8	-	-	-	-	-	-	-
			14	' (AUC)	250	208.6	193	423.7	784.6	1066.8	741.7	689.5	359.2	303.3	220	197	167
			18	Equoral	250	209.7	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	218.6	-	248.3	-	771.8	-	-	-	-	-	-	-
			28	' (AUC)	250	187.2	423	767.9	620.3	529.2	498.4	604.7	418.2	279.9	225.5	216.9	192.5
			35	Neoral	250	196.3	-	-	-	-	-	-	-	-	-	-	-
3		Y-A	-7	Neoral	200	169	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	173	-	384	-	491	-	-	-	-	-	-	-
			14	' (AUC)	200	173.8	174.4	261.2	783.7	1067.8	840.6	542.1	276.8	304.1	199.8	225	137.4
			18	Equoral	200	160	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	218	-	248	-	771	-	-	-	-	-	-	-
			28	' (AUC)	200	118.3	276.7	741.4	1240.6	1058.4	498.4	513.3	348.9	289	177.8	178.8	143.5
			35	Neoral	200	182	-	-	-	-	-	-	-	-	-	-	-
4	3	M-D	-7	Neoral	250	248	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	230.4	-	833.3	-	715.2	-	-	-	-	-	-	-
			14	' (AUC)	250	208.5	337.9	1156.8	473.3	774.1	561.7	396.6	333.4	267.6	210.9	197.6	173.6
			18	Equoral	250	201	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	237.4	-	237.8	-	418.1	-	-	-	-	-	-	-
			28	' (AUC)	250	177.5	199.9	1099	746.2	882.9	525.9	358.8	468.9	374.9	272.6	209.6	187.6
			35	Neoral	250	254	-	-	-	-	-	-	-	-	-	-	-
5	3	D-S	-7	Neoral	200	128	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	127	-	167	-	532	-	-	-	-	-	-	-
			14	' (AUC)	200	201	186	807	1019	999	512	339	261	180	140	119	105
			18	Equoral	200	132	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	125	-	787	-	861	-	-	-	-	-	-	-
			28	' (AUC)	200	186	192	795	996	916	623	382	271	176	145	126	116
			35	Neoral	200	163	-	-	-	-	-	-	-	-	-	-	-
6	3	Y-T	-7	Neoral	400	147	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	400	214	-	965	-	825	-	-	-	-	-	-	-
			14	' (AUC)	400	207	195	522	713	1026	998	696	481	445	308	264	206
			18	Equoral	400	158	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	400	214	-	965	-	825	-	-	-	-	-	-	-
			28	' (AUC)	400	286	1179	981	898	404	320	295	239	168	160	138	146
			35	Neoral	400	142	-	-	-	-	-	-	-	-	-	-	-
7	3	O-B	-7	Neoral	350	151.5	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	350	132	-	94	-	815	-	-	-	-	-	-	-
			14	' (AUC)	350	143	214	679.4	950	1052	823	530	342	242	196	142	121
			18	Equoral	350	141	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	350	183	-	513	-	810	-	-	-	-	-	-	-
			28	' (AUC)	350	164	153	260	748.2	903.2	693.4	502.3	367.9	319.2	218.6	165.6	139.6
			35	Neoral	350	144	-	-	-	-	-	-	-	-	-	-	-

8	3	S-G	-7	Neural	500	178	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	500	168.4	-	896	-	785	-	-	-	-	-	-	-
			14	" (AUC)	500	182	226	688.4	948	1104	894	586	306	262	188	162	148
			18	Equoral	500	270	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	500	178	-	682	-	925	-	-	-	-	-	-	-
			28	" (AUC)	500	186	179	282	826	1006	726	582	385	306	225	182	176
			35	Neural	500	157	-	-	-	-	-	-	-	-	-	-	-
9	3	B-J	-7	Neural	200	144	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	166	-	582	-	896	-	-	-	-	-	-	-
			14	" (AUC)	200	185	236	728.6	985	1091	846	526	381	232	188	179	165
			18	Equoral	200	188	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	176	-	621	-	927	-	-	-	-	-	-	-
			28	" (AUC)	200	166	178	272	786	912	725	516	397	342	261	197	176
			35	Neural	200	156	-	-	-	-	-	-	-	-	-	-	-
10	8	Y-Y	-7	Neural	400	203	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	400	248	-	1096	-	921	-	-	-	-	-	-	-
			14	" (AUC)	400	185	226	728	1106	872	852	341	271	199	158	147	132
			18	Equoral	400	209	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	400	188	-	612	-	975	-	-	-	-	-	-	-
			28	" (AUC)	400	249	199	682	975	1091	850	586	425	326	225	191	156
			35	Neural	400	165	-	-	-	-	-	-	-	-	-	-	-

14-Jan-2004

Center No. 4 (Karachi, Pakistan)

S.No.	C.No.	Sub-init.	Day	Drug	Dose	Trough level	30 m.	1 hr	1/30h	2 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h
1	4	DM	-7	Neoral	150	150	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	102	-	548	-	842	-	-	-	-	-	-	-
			14	' (AUC)	150	141	97	356	562	454	478	408	292	221	146	100	98
			18	Equoral	150	96	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	114	-	238	-	622	-	-	-	-	-	-	-
			28	" (AUC)	150	125	125	190	546	884	522	377	236	196	151	105	808
			35	Neoral	150	135	-	-	-	-	-	-	-	-	-	-	-
2	4	ZR	-7	Neoral	100	202	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	247	-	946	-	682	-	-	-	-	-	-	-
			14	' (AUC)	100	121	142	824	908	658	564	236	220	198	178	150	127
			18	Equoral	100	157	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	123	-	140	-	932	-	-	-	-	-	-	-
			28	" (AUC)	100	143	143	370	608	824	556	365	282	250	196	141	134
			35	Neoral	100	192	-	-	-	-	-	-	-	-	-	-	-
3	4	OZ	-7	Neoral	100	215	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	108	-	454	-	914	-	-	-	-	-	-	-
			14	' (AUC)	100	110	140	588	782	668	628	288	262	213	125	100	89
			18	Equoral	100	79	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	101	-	314	-	580	-	-	-	-	-	-	-
			28	" (AUC)	100	111	109	404	916	726	518	390	262	202	122	97	91
			35	Neoral	100	143	-	-	-	-	-	-	-	-	-	-	-
4	4	Khairun-	-7	Neoral	300	1612	-	-	-	-	-	-	-	-	-	-	-
		nia	0	Follow-up	300	447	-	742	-	1808	-	-	-	-	-	-	-
			14	' (AUC)	300	371	362	490	1032	1584	1298	1134	784	594	454	373	344
			18	Equoral	300	434	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	300	387	-	1578	-	1592	-	-	-	-	-	-	-
			28	" (AUC)	300	446	407	378	384	748	814	564	493	496	556	320	325
			35	Neoral	250	406	-	-	-	-	-	-	-	-	-	-	-
5	4	MW	-7	Neoral	150	554	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	125	-	1012	-	736	-	-	-	-	-	-	-
			14	' (AUC)	150	82	264	1116	752	646	414	292	300	221	139	112	101
			18	Equoral	150	111	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	93	-	912	-	678	-	-	-	-	-	-	-
			28	" (AUC)	150	80	806	1046	774	442	360	282	283	218	126	108	103
			35	Neoral	150	150	-	-	-	-	-	-	-	-	-	-	-
6	4	MS	-7	Neoral	200	266	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	272	-	476	-	720	-	-	-	-	-	-	-
			14	' (AUC)	200	275	252	266	348	630	724	494	457	346	241	236	196
			18	Equoral	200	284	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	303	-	373	-	884	-	-	-	-	-	-	-
			28	" (AUC)	200	340	279	810	916	912	692	560	394	341	243	248	232
			35	Neoral	150	194	-	-	-	-	-	-	-	-	-	-	-
7	4	SA	-7	Neoral	300	296	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	300	296	-	568	-	962	-	-	-	-	-	-	-
			14	' (AUC)	300	114	283	922	1238	1148	930	610	543	485	362	289	248
			18	Follow-up	300	210	-	-	-	-	-	-	-	-	-	-	-

14-Jan-2004

			21	Equal	300	260	-	198	-	1146	-	-	-	-	-	-	-
			28	" (AUC)	300	452	375	328	452	716	754	829	613	329	377	286	376
			35	Neural	250	287	-	-	-	-	-	-	-	-	-	-	-
8	4	MA	-7	Neural	150	210	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	257	-	528	-	1066	-	-	-	-	-	-	-
			14	" (AUC)	180	180	208	354	732	1030	686	428	368	304	187	156	151
			18	Equal	150	214	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	177	-	201	-	908	-	-	-	-	-	-	-
			28	" (AUC)	150	266	208	222	366	944	1008	762	334	384	280	270	282
			35	Neural	150	258	-	-	-	-	-	-	-	-	-	-	-
9	4	MJ	-7	Neural	300	208	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	300	198	-	466	-	1046	-	-	-	-	-	-	-
			14	" (AUC)	300	266	289	938	1088	1052	592	426	374	329	192	141	137
			18	Equal	300	261	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	300	211	-	420	-	960	-	-	-	-	-	-	-
			28	" (AUC)	300	219	185	284	1082	1354	1172	762	462	354	289	215	176
			35	Neural	300	225	-	-	-	-	-	-	-	-	-	-	-
10	4	SH	-7	Neural	200	152	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	198	-	1602	-	1006	-	-	-	-	-	-	-
			14	" (AUC)	200	241	519	1196	1084	838	594	397	356	339	226	204	190
			18	Equal	200	211	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	174	-	694	-	956	-	-	-	-	-	-	-
			28	" (AUC)	200	219	515	1260	1064	966	662	375	348	294	247	203	152
			35	Neural	175	182	-	-	-	-	-	-	-	-	-	-	-
11	4	IK	-7	Neural	100	120	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	76	-	314	-	626	-	-	-	-	-	-	-
			14	" (AUC)	100	97	96	180	466	362	288	170	145	126	83	76	55
			18	Equal	100	94	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	73	-	244	-	388	-	-	-	-	-	-	-
			28	" (AUC)	100	153	163	744	702	520	338	213	197	146	113	89	98
			35	Neural	100	64	-	-	-	-	-	-	-	-	-	-	-
12	4	Shahzad	-7	Neural	150	122	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	125	242	-	720	-	448	-	-	-	-	-	-	-
			14	(AUC)	125	356	232	620	912	744	562	447	376	323	279	185	176
			18	Equal	125	173	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	125	87	-	58	-	85	-	-	-	-	-	-	-
			28	(AUC)	125	201	190	201	304	467	607	409	383	314	202	134	119
			35	Neural	125	108	-	-	-	-	-	-	-	-	-	-	-
13	4	SF	-7	Neural	200	132	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	196	-	341	-	584	-	-	-	-	-	-	-
			14	(AUC)	150	157	134	184	452	540	424	265	227	170	123	100	76
			18	Equal	150	80	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	180	202	-	209	-	262	-	-	-	-	-	-	-
			28	(AUC)	150	205	176	192	295	906	261	241	220	146	142	111	81
			35	Neural	180	142	-	-	-	-	-	-	-	-	-	-	-
14	4	AJ	-7	Neural	125	58	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	125	223	-	250	-	320	-	-	-	-	-	-	-
			14	(AUC)	100	105	94	76	260	452	420	307	198	166	97	73	74
			18	Equal	100	79	-	-	-	-	-	-	-	-	-	-	-

14-Jan-2004

			21	Follow-up	100	79	-	90	-	271	-	-	-	-	-	-	-
			28	(AUC)	100	112	90	99	102	130	156	238	187	178	162	116	75
			35	Neural	100	118	-	-	-	-	-	-	-	-	-	-	-
15	4	Imada	-7	Neural	150	77	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	288	-	728	-	600	-	-	-	-	-	-	-
			14	(AUC)	150	184	334	684	696	628	811	374	276	256	189	149	166
			18	Equoral	150	166	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	173	-	998	-	840	-	-	-	-	-	-	-
			28	(AUC)	150	200	188	523	867	674	433	385	332	278	233	188	164
			35	Neural	150	193	-	-	-	-	-	-	-	-	-	-	-
16	4	MA	-7	Neural	100	86	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	107	-	402	-	422	-	-	-	-	-	-	-
			14	(AUC)	100	77	62	117	179	188	166	118	95	131	84	76	57
			18	Equoral	100	50	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	91	-	181	-	395	-	-	-	-	-	-	-
			28	(AUC)	100	78	86	138	246	226	232	189	147	127	117	86	71
			35	Neural	100	124	-	-	-	-	-	-	-	-	-	-	-
17	4	Yasmeen	-7	Neural	175	142	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	175	167	-	797	-	605	-	-	-	-	-	-	-
			14	(AUC)	150	107	270	482	883	434	354	264	213	167	106	98	70
			18	Equoral	150	114	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	114	-	304	-	606	-	-	-	-	-	-	-
			28	(AUC)	150	120	360	998	778	770	436	307	246	188	121	99	96
			35	Neural	150	86	-	-	-	-	-	-	-	-	-	-	-
18	4	SB	-7	Neural	125	81	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	125	65	-	337	-	403	-	-	-	-	-	-	-
			14	(AUC)	125	47	146	436	388	346	437	170	136	117	81	49	31
			18	Equoral	125	68	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	125	63	-	169	-	277	-	-	-	-	-	-	-
			28	(AUC)	125	65	59	389	633	688	430	274	178	119	98	72	60
			35	Neural	125	49	-	-	-	-	-	-	-	-	-	-	-
19	4	RK	-7	Neural	100	180	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	100	227	-	567	-	568	-	-	-	-	-	-	-
			14	(AUC)	100	185	275	496	541	527	435	368	276	221	181	160	140
			18	Equoral	100	234	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	100	216	-	743	-	794	-	-	-	-	-	-	-
			28	(AUC)	100	200	176	209	328	349	443	465	344	329	244	181	178
			35	Neural	100	176	-	-	-	-	-	-	-	-	-	-	-
20	4	Shahraz	-7	Neural	150	180	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	181	-	169	-	407	-	-	-	-	-	-	-
			14	(AUC)	125	104	136	229	334	399	242	381	266	236	152	113	90
			18	Equoral	125	151	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	125	136	-	280	-	503	-	-	-	-	-	-	-
			28	(AUC)	125	132	174	457	609	636	525	353	261	257	169	130	113
			35	Neural	125	120	-	-	-	-	-	-	-	-	-	-	-

Center No. 5 (Rayak Hospital, Beirut, Lebanon)

S.No.	C.No.	Subjct.	Day	Drug	Dose	Trough level	30 min.	1 hr	1/30th	1 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h
1	5	AH	-7	Neoral	250	288.5	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	193	-	514.2	-	647	-	-	-	-	-	-	-
			14	' (AUC)	250	254	295	526	684	794	698	570	411	363	265	264	234
			18	Equoral	250	262.7	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	208	-	310	-	804.6	-	-	-	-	-	-	-
			28	' (AUC)	250	293	509	1371	993	618	498	415	371	291	260	237	169
			35	Neoral	250	263	-	-	-	-	-	-	-	-	-	-	-
2	5	ZCh	-7	Neoral	200	142	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	96	-	408	-	854	-	-	-	-	-	-	-
			14	' (AUC)	200	94	296	538	806	990	908	275	202	160	144	70	94
			18	Equoral	200	119	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	106	-	1011	-	305	-	-	-	-	-	-	-
			28	' (AUC)	200	119	112	237	612	505	348	296	177	150	128	113	105
			35	Neoral	200	149	-	-	-	-	-	-	-	-	-	-	-
3	5	MH	-7	Neoral	250	183	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	119.8	-	483	-	820	-	-	-	-	-	-	-
			14	' (AUC)	250	101	264	784	725	533	332	250	189	147	145	110	88
			18	Equoral	250	153	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	151	-	854	-	743	-	-	-	-	-	-	-
			28	' (AUC)	250	138	182	574	614	667	667	461	391	294	206	190	133
			35	Neoral	250	198	-	-	-	-	-	-	-	-	-	-	-
4	5	IJ	-7	Neoral	200	169	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	168	-	910	-	598	-	-	-	-	-	-	-
			14	' (AUC)	200	168.9	178	257	362	565	649	740	486	316	257	222	194
			18	Equoral	200	177	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	198	-	474	-	745	-	-	-	-	-	-	-
			28	' (AUC)	200	194	188	847	1196	1072	714	491	415	337	285	231	215
			35	Neoral	200	155	-	-	-	-	-	-	-	-	-	-	-
5	5	KS	-7	Neoral	300	317.4	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	300	363	-	883	-	865	-	-	-	-	-	-	-
			14	' (AUC)	300	324	800	1351	1373	1226	915	688	830	474	386	416	362
			18	Equoral	300	361	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	300	323	-	1297	-	960	-	-	-	-	-	-	-
			28	' (AUC)	300	390	584	1327	1195	1141	961	692	567	483	423	400	354
			35	Neoral	300	334	-	-	-	-	-	-	-	-	-	-	-
6	5	GN	-7	Neoral	150	114	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	128	-	471	-	687	-	-	-	-	-	-	-
			14	' (AUC)	150	114	198	376	580	640	426	369	221	190	267	184	109
			18	Equoral	150	123	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	122	-	396	-	655	-	-	-	-	-	-	-
			28	' (AUC)	150	113	204	388	568	661	421	354	211	200	189	163	128
			35	Neoral	150	121	-	-	-	-	-	-	-	-	-	-	-
7	5	JK	-7	Neoral	150	178	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	157	-	530	-	332	-	-	-	-	-	-	-
			14	' (AUC)	150	178	204	518	679	573	498	425	389	331	283	232	203
			18	Equoral	150	136	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	178	-	501	-	561	-	-	-	-	-	-	-
			28	' (AUC)	150	192	215	511	661	532	471	409	364	306	269	215	174
			35	Neoral	150	178	-	-	-	-	-	-	-	-	-	-	-

			35	Normal	150	156	-	-	-	-	-	-	-	-	-	-	-	-
	5	SD	-7	Normal	250	239	-	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	250	249	-	612	-	963	-	-	-	-	-	-	-	-
			14	" (AUC)	250	239	311	643	1119	1170	897	671	536	493	401	343	266	-
			18	Equival	250	246	-	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	250	239	-	653	-	962	-	-	-	-	-	-	-	-
			28	" (AUC)	250	245	903	652	1003	963	873	643	513	456	411	329	261	-
			35	Normal	250	251	-	-	-	-	-	-	-	-	-	-	-	-
9	5	AM	-7	Normal	150	101	-	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	150	110	-	272	-	482	-	-	-	-	-	-	-	-
			14	" (AUC)	150	101	199	231	455	498	356	316	283	231	199	146	122	-
			18	Equival	150	109	-	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	150	101	-	236	-	497	-	-	-	-	-	-	-	-
			28	" (AUC)	150	97	132	240	419	482	325	309	278	229	175	147	109	-
			35	Normal	150	96	-	-	-	-	-	-	-	-	-	-	-	-
10	5	AH	-7	Normal	200	71	-	-	-	-	-	-	-	-	-	-	-	-
			0	Follow-up	200	57	-	143	-	304	-	-	-	-	-	-	-	-
			14	" (AUC)	200	71	109	165	301	576	315	289	227	187	150	106	89	-
			18	Equival	200	61	-	-	-	-	-	-	-	-	-	-	-	-
			21	Follow-up	200	65	-	162	-	287	-	-	-	-	-	-	-	-
			28	" (AUC)	200	68	107	145	192	344	310	263	210	157	98	101	83	-
			35	Normal	200	77	-	-	-	-	-	-	-	-	-	-	-	-

Equoral[®] capsules

16. Appendices

16.2 Subject Data Listings

16.2.6 Individual Efficacy Response Data

Equoral[®] capsules

16.2.6 Individual Efficacy Response Data

Not applicable

16. Appendices**16.2 Patient Data Listings****16.2.7 Adverse Event Listings (Each Patient)**

Equoral® capsules

16.2.7 ADVERSE EVENTS LISTINGS BY PATIENT**Subject No. 1, centre No. 1**

Age: 46
 Race: Caucasian
 Sex: Male
 Weight: 69.6
 Study period: II, III

Day	2-16
Month	10
Year	2002
Day of study	21-35
Event observed	Oral thrush
Onset time	2.10.2002
End time	16.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	15 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Recovered

Subject No. 3, centre No. 1

Age: 36
 Race: Caucasian
 Sex: Male
 Weight: 126
 Study period: II, III

Day	2-16
Month	10
Year	2002
Day of study	21-35
Event observed	Oral thrush
Onset time	2.10.2002
End time	16.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	15 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Recovered

Equoral® capsules

Subject No. 5, centre No. 1

Age: 62
 Race: Caucasian
 Sex: Male
 Weight: 76
 Study period: II, III

Day	8-16
Month	10
Year	2002
Day of study	27-35
Event observed	Oral thrush
Onset time	8.10.2002
End time	16.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	9 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Recovered

Subject No. 6, centre No. 1

Age: 47
 Race: Caucasian
 Sex: Male
 Weight: 55
 Study period: II, III

	Day 2-16 Month 10 Year 2002 Day of study 21-35	Day 8-10 Month 10 Year 2002 Day of study 27-29	Day 6-10 Month 10 Year 2002 Day of study 25-29
Event observed	Oral thrush	Red right eye	Itching exacerbation at night mainly
Onset time	2.10.2002	8.10.2002	6.10.2002
End time	16.10.2002	10.10.2002	10.10.2002
Intensity	Moderate	Moderate	Mild
Appearance	Continuous	Isolated	Intermittent
Duration	15 days	3 days	5 days
Serious	No	No	No
Event causality	Test drug		
Relation to the test drug	Probable	Possible	Possible
Action taken study (drug dose)	None	None	None
Action taken (therapeutic medication)	No	No	No
Outcome	Recovered	Ongoing	Ongoing
Comments	White tongue was found on day 0		

Subject No. 7, centre No. 1

Age: 25
 Race: Caucasian
 Sex: Female
 Weight: 52
 Study period: II

Day	3-10
Month	10
Year	2002
Day of study	21-28
Event observed	Oral thrush
Onset time	3.10.2002
End time	10.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	8 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Recovered
Comments	White tongue was found on day -7

Subject No. 8, centre No. 1

Age: 35
 Race: Caucasian
 Sex: Male
 Weight: 67.5
 Study period: II, III

Day, month	30.9. - 17.10.
Year	2002
Day of study	18-35
Event observed	Oral thrush
Onset time	30.9.2002
End time	17.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	18
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Recovered
Comments	White tongue was found on day -7 and day 0

Equoral[®] capsules

Subject No. 9, centre No. 1

Age: 25
 Race: Caucasian
 Sex: Female
 Weight: 55.5
 Study period: II, III

Day	30	30	3-17
Month	9	9	10
Year	2002	2002	2002
Day of study	18	18	21-35
Event observed	Headache	Epistaxis	Oral thrush
Onset time	29.9.2002	29.9.2002	3.10.2002
End time	29.9.2002	29.9.2002	17.10.2002
Intensity	Severe	Mild	Moderate
Appearance	Intermittent	Isolated	Continuous
Duration	1 day	1 day	15 days
Serious	No	No	No
Event causality	Cocurrent disease	Cocurrent disease	Test drug
Relation to the test drug	None	None	Probable
Action taken study (drug dose)	None	None	None
Action taken (therapeutic medication)	No	No	No
Outcome	Recovered	Recovered	Ongoing
Comments	White tongue was found on day -7		

Subject No. 10, centre No. 1

Age: 37
 Race: Caucasian
 Sex: Female
 Weight: 57.5
 Study period: II, III

Day	11-17
Month	10
Year	2002
Day of study	29-35
Event observed	Oral thrush
Onset time	11.10.2002
End time	17.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	7 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Recovered

Equoral® capsules

Subject No. 11, centre No. 1

Age: 29
 Race: Caucasian
 Sex: Male
 Weight: 79
 Study period: II, III

Day	3-17
Month	10
Year	2002
Day of study	21-35
Event observed	Oral thrush
Onset time	3.10.2002
End time	17.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	15 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Recovered

Subject No. 12, centre No. 1

Age: 29
 Race: Caucasian
 Sex: Male
 Weight: 79
 Study period: II, III

Day	1-18
Month	10
Year	2002
Day of study	18-35
Event observed	Oral thrush
Onset time	1.10.2002
End time	18.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	18 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Ongoing

Equoral[®] capsules**Subject No. 13, centre No. 1**

Age: 33
 Race: Caucasian
 Sex: Male
 Weight: 70.5
 Study period: II, III

Day	4-18
Month	10
Year	2002
Day of study	21-35
Event observed	Oral thrush
Onset time	4.10.2002
End time	18.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	15 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Ongoing

Subject No. 14, centre No. 1

Age: 29
 Race: Caucasian
 Sex: Female
 Weight: 56
 Study period: screening, I, II, III

Day	6.9.- 18.10.	4-18.10.
Year	2002	2002
Day of study	-7-35	21-35
Event observed	Gingival hypertrophy	Oral thrush
Onset time	6.9.2002	4.10.2002
End time	18.10.2002	18.10.2002
Intensity	Severe	Moderate
Appearance	Continuous	Continuous
Duration	43 days	15 days
Serious	No	No
Event causality	Test drug	Test drug
Relation to the test drug	Probable	Probable
Action taken study (drug dose)	None	None
Action taken (therapeutic medication)	No	No
Outcome	Ongoing	Recovered

Subject No. 15, centre No. 1

Age: 54
Race: Caucasian
Sex: Male
Weight: 62
Study period: II, III

Day	1-18
Month	10
Year	2002
Day of study	18-35
Event observed	Oral thrush
Onset time	1.10.2002
End time	18.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	18 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Ongoing
Comments	White tongue was found on day -7

Subject No. 16, centre No. 1

Age: 43
Race: Caucasian
Sex: Female
Weight: 78
Study period: II, III

Day	1-18
Month	10
Year	2002
Day of study	18-35
Event observed	Oral thrush
Onset time	1.10.2002
End time	18.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	18 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Ongoing
Comments	White tongue was found on day -7 and day 0

Equoral® capsules

Subject No. 17, centre No. 1

Age: 39
 Race: Caucasian
 Sex: Male
 Weight: 61
 Study period: II, III

Day	1-18
Month	10
Year	2002
Day of study	18-35
Event observed	Oral thrush
Onset time	1.10.2002
End time	18.10.2002
Intensity	Moderate
Appearance	Continuous
Duration	18 days
Serious	No
Event causality	Test drug
Relation to the test drug	Probable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Ongoing

Subject No. 18, centre No. 1

Age: 45
 Race: Caucasian
 Sex: Male
 Weight: 77.5
 Study period: II

Day	28.1.-14.2.
Month	1
Year	2003
Day of study	18-35
Event observed	White tongue
Onset time	28.1.2003
End time	14.2.2003
Intensity	Mild
Appearance	Continuous
Duration	18 days
Serious	No
Event causality	Test drug
Relation to the test drug	Not Assessable
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Ongoing

Subject No. 20, centre No. 1

Age: 34
Race: Caucasian
Sex: Female
Weight: 64.6
Study period: II

Day	1-15
Month	2
Year	2003
Day of study	21-35
Event observed	Oral thrush
Onset time	1.2.2003
End time	15.2.2003
Intensity	Mild
Appearance	Isolated
Duration	15 days
Serious	No
Event causality	Study indication
Relation to the test drug	Possible
Action taken study (drug dose)	None
Action taken (therapeutic medication)	No
Outcome	Ongoing

Subject No. 7, centre No. 4

Age: 33
Race: Asian
Sex: Male
Weight: 50
Study period: I

Day	14
Month	2
Year	2003
Day of study	13
Event observed	Fever
Onset time	14.2.2003
End time	14.2.2003
Intensity	Moderate
Appearance	Isolated
Duration	1 day
Serious	No
Event causality	Cocurrent disease
Relation to the test drug	None
Action taken study (drug dose)	No
Action taken (therapeutic medication)	No
Outcome	Recovered

16. Appendices

16.2 Patient Data Listings

16.2.8 Listing of Individual Laboratory Measurements by Patient, when required by Regulatory Authorities

Equoral[®] capsules

16.2.8 LISTING OF INDIVIDUAL LABORATORY MEASUREMENT BY PATIENT

16.2.8.1 HEMATOLOGY

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	1	1	49	15.7	5.41	6.47	62	1	1	29	5.8	246
-21	1	1	47.2	15.6	5.2	6.48	63	0.7	1.4	28.5	5.3	211

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	2	1	33.3	11.6	4.18	10.25	67.8	0.8	1.5	23.7	4.7	309
21	2	1	32.6	11.1	3.87	7.56	63.3	1.4	2.6	25.7	5.6	314

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	3	1	36.1	12.1	4.14	9.92	61	0.9	1.8	28.4	5	221
21	3	1	34.3	11.5	3.91	8.1	60.4	0.8	2.1	28.6	5.8	216

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	4	1	38.2	12.1	3.47	6.54	73.2	1	2.9	14.3	6.6	174
21	4	1	34	11.2	3.12	5.11	70.9	1.3	2.4	16.2	7.2	154

Equoral® capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	5	1	43	13	3.81	9.93	73.6	0.7	1.2	15.8	7.1	272
21	5	1	37.6	12.1	3.88	7.99	72	0.8	1.9	18	7.3	235

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	6	1	49.9	15.8	5.73	10.13	77.1	0.6	1.5	14.7	5.4	226
21	6	1	46.2	15.2	5.52	10.55	75.8	0.6	2.5	15.1	5.2	210

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	7	1	37.9	12.3	4.18	9.02	54.2	0.5	1.5	38.2	4.2	353
21	7	1	35.7	11.7	3.97	9.57	58.8	0.5	1	33.3	5.3	355

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	8	1	41	13.5	4.43	10.27	55.3	0.5	1.3	35	6.2	263
21	8	1	39.6	13	4.29	9.42	54.1	0.6	1.5	32	8.9	229

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	9	1	32.9	10.9	3.83	7.38	67	0.5	1.4	24.8	4.4	317
21	9	1	31.5	10.7	3.68	7.33	69.5	0.5	1.4	23.2	4.1	285

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	10	1	38.2	13	4.32	5.71	59	0.4	2.6	30.6	5.6	332
21	10	1	38	12.5	4.14	6.48	62.1	0.5	2.1	27.5	6.5	281

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	11	1	37.6	12.7	3.86	3.63	55.4	0.3	1.4	35.6	5.5	215
21	11	1	36.8	12.4	3.78	3.81	53.9	0.4	2.3	35	6.2	201

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	12	1	39.2	12.9	4.41	5.95	61.9	0.8	1.9	26.9	6.9	313
21	12	1	40.4	13.1	4.5	7.35	70.1	0.4	1.3	21.1	5.7	306

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	13	1	37.1	12.6	4.13	7.91	55.3	0.5	2.1	36.1	4.7	279
21	13	1	35.2	12.2	3.93	6.34	51.7	0.4	2.3	36.2	7.2	280

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	14	1	38.8	9.9	2.73	5.73	70.8	0.6	2.9	19.8	5.1	330
21	14	1	26.9	9.2	2.54	5.61	74.7	0.7	2.5	16.2	4.7	298

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	15	1	34.4	11.9	4.03	5.44	64.6	0.4	2.3	24.8	5.2	186
21	15	1	32.6	11.3	3.71	4.79	63.8	0.6	4.3	23.7	5.5	186

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	16	1	39.9	13.1	4.35	4.72	63.2	0.3	2.9	27	5.5	210
21	16	1	39.9	13	4.34	3.87	53.8	0.3	2.4	36.7	5.2	188

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	17	1	47.5	16.3	5.09	6.58	77.2	0.1	0.5	16.1	4.5	219
21	17	1	47.1	16.4	5.04	6.97	75.3	0.3	0.2	19.1	4.5	232

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	18	1	44.5	15	5	6.18	74.3	0.3	0.5	18	4.3	221
21	18	1	44	15	5.1	6.2	76	0.3	0.6	18	4	219

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	19	1	39.4	14	5.1	6.4	43	0.5	1	24.3	3	160
21	19	1	41.2	14	4.7	6.45	53	0.5	0.6	24.4	4	165

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	20	1	37	12.1	6.6	6.94	40	0.1	1	22.3	3	193
21	20	1	ND	ND	ND	6.89	ND	ND	ND	26.3	ND	ND

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	21	1	42.5	13	4.8	8.4	60	1	1	37	3	210
21	21	1	43	13.2	5.8	8.24	60.5	1	0.8	34.5	2	214

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	22	1	43	14.5	6.1	4.8	53	0.1	0.5	32	3	220
21	22	1	45	14.3	6.2	4.7	55	0.1	0.5	32	3	225

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	23	1	46	14	6.6	9.4	56	0.2	0.1	27	2	194
21	23	1	46	14.1	6.3	9.3	52	0.2	0.5	26	2	210

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	24	1	41	13	5.8	6.5	66	0.4	0.5	8	3	215
21	24	1	41.5	13.2	5.9	6.3	68	0.2	0.5	11.2	2.2	220

Equoral® capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	25	1	40	14	4	9.8	51	0.6	0.3	38	2.2	230
21	25	1	40	15	6.2	9.7	56	0.4	0.2	32.6	2.1	233

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	26	1	43	13.6	5.4	6	54	0.2	0.4	10	2	215
21	26	1	44	13.3	6.3	6	64	0.1	0.2	12	2.1	225

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	27	1	39	12	4.8	3.9	68	0.4	0.1	12	2.4	196
21	27	1	38	12.1	4.58	3.74	69	1	0.3	18.7	2.3	192

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	28	1	41	13	5.1	6.4	57	0.4	0.2	17.5	2.1	210
21	28	1	42	13.1	6.1	6.54	68	0.3	0.2	19	2	215

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	29	1	41.5	13.6	4.7	6.4	61	0.1	0.3	14	2	215
21	29	1	42	13.6	5.6	6.5	62	0.3	1.1	13.4	2	230

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	30	1	42.3	14.1	5.4	6.6	59	0.4	1	29	2	230
21	30	1	38.6	13.8	5.4	6.6	59	0.3	1	29	2	222

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	1	3	53	18.3	6.42	8.83	57.6	0.44	1.62	15.3	10.4	197
21	1	3	51.2	17.4	5.9	7.4	58.8	0.3	1.6	18.2	21.1	186

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	2	3	48.6	16.9	5.89	9.27	77.7	0.37	0.51	12.4	9	290
21	2	3	47.7	16.8	5.82	8.8	78.5	0.3	0.4	8.2	12.6	276

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	1	4	39.7	13	3.72	7.64	73.3	0.26	1.57	19.37	5.5	186
21	1	4	41	14	4.3	4.5	61.3	0.4	1.8	31.6	4.9	128

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	2	4	40.9	12.7	3.96	9.67	57.4	0.3	2.7	34	5.6	266
21	2	4	37	12	3.8	5.8	70.4	0.7	1.4	22.1	5.4	245

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	3	4	38	12.4	3.77	6.63	63.9	0.5	1.2	24.9	9.5	231
21	3	4	36	11.9	3.5	6.3	70.3	0.3	1.9	20.7	6.8	245

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	4	4	39.1	11.3	3.67	7.76	73.1	0.5	0.9	18.3	7.2	293
21	4	4	37	12	3.8	5.8	70.4	0.7	1.4	22.1	5.4	245

Equoral® capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	5	4	46	13.9	5.13	14.5	64.9	0.4	0.3	28.8	5.5	248
21	5	4	42	13.3	4.9	14	60	0.4	1.4	31.7	6.5	230

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	6	4	30.3	9.6	2.82	4.29	74	0.2	0.7	17.9	7.2	183
21	6	4	31.7	10.1	2.97	7.55	73	0	1	15	9	200

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	7	4	47	15.4	4.6	7.7	77.2	0.3	0.9	9.9	11.7	169
21	7	4	51.24	16.4	4.97	5.6	71.43	0.71	1.79	13.21	12.86	252

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	8	4	39.6	12.6	4.04	4.61	69.1	0.2	0.7	21.5	8.5	293
21	8	4	45.2	11.6	3.6	3.9	68.42	0.26	0.79	21.05	9.47	272

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	9	4	38.9	12.7	4.09	6.8	66.8	0.6	1.6	25.6	5.4	176
21	9	4	38	12.4	3.97	7.02	66.6	0.4	2.1	25.1	5.8	162

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	10	4	42	13.3	4.6	5.99	66.5	0.5	1.3	23	8.8	280
21	10	4	41	13.1	4.5	6.6	67.6	0.5	1.1	23.8	7.0	235

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	11	4	44	13.2	4.8	6.2	49	0.6	1.4	40	8.5	248
21	11	4	43	13.1	4.8	6.3	42.7	0.2	1	48.2	7.9	230

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	12	4	38	9.8	3.8	5.1	58.5	0.2	2	31.4	7.9	219
21	12	4	31.6	9.6	3.84	5.91	54.7	0.3	2	37.2	5.8	217

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	13	4	38	11.3	3.8	12.5	73.3	0.4	1	20.3	4	481
21	13	4	39	12.6	4.14	7.12	57.4	0.6	2	33.8	6.2	296

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	14	4	38	8	2.9	6.6	67.7	0.5	1.5	26.2	4.1	339
21	14	4	38.7	8.9	2.77	7.67	62.9	0.4	1.8	29.6	5.3	288

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	15	4	37	7.8	2.2	4.7	53.9	0.4	1.1	34.3	10.3	203
21	15	4	33.9	9.1	3.72	5.68	43	0.5	1.6	46.3	8.6	243

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	16	4	39.5	12.9	4.07	7.51	62.6	0.8	2.1	27.7	6.8	180
21	16	4	39.8	12.9	4.1	6.34	66.5	0.5	2.4	25.6	5	143

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	17	4	34.5	11.1	3.68	7.12	46.1	0.7	9.7	37.2	6.3	263
21	17	4	33	10.4	3.63	6.3	47.5	0.6	10.8	35.1	6	258

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	18	4	34.3	10.9	3.68	7.36	62	0.5	3.3	28.9	4.3	127
21	18	4	33	10.2	3.4	10.5	66.4	0.5	3.4	26.1	3.6	124

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	19	4	38.6	12.8	5	9.14	63.3	0.2	1	28.3	7.2	189
21	19	4	40	12.7	5.1	7.4	52.7	0.3	1.2	37.9	7.9	157

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	20	4	38.2	10.9	4.19	5.38	58.1	0.2	1.7	30.9	9.1	159
21	20	4	35	10.7	4.1	4.9	63.8	0.2	1.2	26.9	7.9	130

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	1	5	38	11.9	4.9	8.9	58	0.4	1.4	29.1	6.5	224
21	1	5	55	12.9	5.13	8.6	53.2	0.4	0.8	28.8	5.5	248

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	2	5	40	13	4.1	5.5	63	0.4	1.8	26	4.9	172
21	2	5	44	13.5	3.92	5.2	63.7	0.5	1.9	25.7	5.3	115

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	3	5	39	12.9	4.3	7.1	59	0.5	3.4	25	4.5	272
21	3	5	37	11.9	3.83	7.3	60.2	0.5	2.3	31.8	5.2	306

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	4	5	41	13.7	3.7	6.3	67.2	0.9	2.4	24.9	4.3	247
21	4	5	40	13.2	3.7	6.3	70.3	0.3	1.9	23.4	6.8	245

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	5	5	40	13.1	3.8	5.2	69	0.7	1.4	20.9	5.4	245
21	5	5	38	12.4	3.91	5.9	63.2	0.6	1.6	21	5.5	276

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	6	5	38	11.9	3.8	6.1	64.5	0.6	1.6	19.7	5.4	209
21	6	5	39.1	12.3	4.21	6.2	64.2	0.5	1.8	18.9	7.3	178

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	7	5	45	14.1	4.5	5.3	71.9	0.4	1.5	15.4	11.9	282
21	7	5	46	15.8	4.83	5.8	73.4	0.5	1.9	13.8	10.4	227

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	8	5	38	11	3.8	8.2	72	0.9	1.3	28	7.1	261
21	8	5	38.3	12.2	3.89	8	68	0.7	0.8	27	7.9	272

Equoral[®] capsules

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	9	5	39	11	4.8	5.7	68	0.5	1.1	19.8	7.9	257
21	9	5	37.5	12.5	3.06	5.79	71	0.7	0.7	18.5	7.2	203

Day	Subject No.	Centre No.	Haematocrit (%)	Haemoglobin (g/dL)	Erythrocytes ($\times 10^{12}/L$)	WBC ($\times 10^9/L$)	Neutrophils (%)	Basophils (%)	Eosinophils (%)	Lymphocytes (%)	Monocytes (%)	Platelets ($\times 10^9/L$)
-7	10	5	44	14.1	4.8	6.2	57	0.6	1.4	23	8.5	248
21	10	5	41	13.1	4.6	6.2	60	0.5	1	24	7.8	228

Value abnormal value

Value clinically significant abnormal value

Equoral[®] capsules

16.2.8.2 BLOOD CHEMISTRY

Subject 1 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	1	1	1.45	38	4.7	23	115	44	280	1.6	136	6.9	
21	1	1	1.63	69	5	23	100	46	338	1.1	167	7.3	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	1	1	85	141	4.5	2	109	9.8	3.5	95	201		
21	1	1	93	144	4.8	2.1	101	10	3.4	119	209		

Subject 2 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	2	1	1.46	54	5.2	23	18	40	144	1.1	52	6.8	
21	2	1	1.32	61	4.8	22	18	46	166	0.7	54	6.5	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	2	1	93	142	4	2	104	9.6	4.3	100	190		
21	2	1	96	142	3.9	2.1	105	9.5	3.8	110	161		

Equoral® capsules

Subject 3 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	3	1	1.76	90	7.6	23	16	26	170	0.8	62	7.3	
21	3	1	4.03	93	8.0	17	12	23	154	0.6	68	7.2	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	3	1	90	136	4.3	2.1	107	9.7	4.2	273	163		
21	3	1	97	138	4.4	2.3	105	9.8	4.5	250	182		
Subject 4 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	4	1	1.3	96	5.3	11	19	60	305	0.6	146	6.2	
21	4	1	1.6	96	6.3	12	13	63	273	0.6	142	6	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	4	1	86	138	5.4	3.6	104	8.3	4.9	98	204		
21	4	1	88	141	5.4	4	104	8	4.6	60	182		

Equoral[®] capsules

Subject 5 - centre 1		Centre No.	Urea (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	5	1	46	1.6	7.8	12	10	17	194	0.7	120	6.5
21	5	1	89	1.62	9.1	15	13	11	190	0.6	123	6.6
Subject		Centre No.	Sodium (mmol/L)	Glucose (mg/dL)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	5	1	144	92	6.1	2.3	104	9.7	3.7	156	199	
21	5	1	143	89	4.7	2.2	104	9.9	3.6	172	158	

Subject 6 - centre 1		Centre No.	Urea (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	6	1	70	1.59	6.6	28	15	60	174	0.8	90	6.8
21	6	1	49	1.64	6.2	43	16	72	182	0.6	113	6.3
Subject		Centre No.	Sodium (mmol/L)	Glucose (mg/dL)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	6	1	139	82	4	1.9	103	9.9	3.3	129	257	
21	6	1	139	84	4.7	2.2	100	9.8	3.6	150	240	

Equoral[®] capsules

Subject 7 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	7	1	1.04	40	4.7	11	14	10	105	0.7	70	7.5	
21	7	1	1.1	44	4.4	10	14	10	108	0.9	64	7.5	
Subject 8 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	7	1	80	141	4.5	2	106	9.9	3	37	192		
21	7	1	80	137	4.2	1.9	101	10.1	3.5	44	210		

Subject 8 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	8	1	1.33	40	6.1	18	17	31	150	0.8	73	6.6	
21	8	1	1.34	51	5.5	18	20	29	132	0.7	83	6.7	
Subject 9 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	8	1	90	142	3.9	2.2	102	9.4	3.9	120	142		
21	8	1	83	140	4.5	2.3	104	9.4	4	125	145		

Equoral[®] capsules

Subject 9 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	9	1	1.19	42	6.6	10	14	13	182	0.8	140	7.1	
21	9	1	1.26	53	6.6	10	13	10	193	1.3	143	7.2	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	9	1	105	139	4.8	2	105	10.3	3.4	60	167		
21	9	1	94	137	4.7	1.8	104	10.3	3.3	67	148		

Subject 10 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	10	1	1	39	5.7	15	12	10	107	0.8	64	6.9	
21	10	1	1.07	44	6.2	16	14	10	110	0.7	70	6.9	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	10	1	91	140	3.8	2.1	102	9.5	3.3	123	175		
21	10	1	89	137	3.9	1.9	104	9.5	3.4	118	154		

Equoral® capsules

Subject 11 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	11	1	1.14	38	4.8	11	29	15	150	0.7	68	8.6	
21	11	1	1.08	34	4.7	11	22	12	160	0.9	82	7.5	
Subject 12 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	11	1	107	141	4.2	2.2	99	9.4	3.6	63	166		
21	11	1	98	138	4.1	2.1	101	9.5	3.5	95	192		
Subject 12 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	12	1	0.89	45	6.1	14	24	11	142	0.5	57	7.3	
21	12	1	0.7	31	4.9	15	20	10	152	0.7	61	7.1	
Subject 12 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	12	1	109	143	3.8	1.9	105	9.8	3.8	122	165		
21	12	1	102	144	4.1	1.9	101	9.6	3.3	143	155		

Equora® capsules

Subject 13 - centre 1												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	13	1	1.45	31	4.5	15	17	15	245	0.6	66	6.4
21	13	1	1.42	31	3.6	26	39	12	238	1.1	58	6.2
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	13	1	91	141	3.9	2.1	105	9.4	3.6	24	151	
21	13	1	85	139	3.8	2.3	101	9.6	3.2	65	138	

Subject 14 - centre 1												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	14	1	1.07	37	3	12	16	11	200	0.8	47	7.6
21	14	1	1.3	43	6.2	10	10	9	196	1.2	48	7.6
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	14	1	91	143	4.6	1.8	102	9.7	3.7	86	152	
21	14	1	89	141	4.2	2	100	9.4	3.1	92	156	

Equoral® capsules

Subject 15 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	15	1	1.33	54	6.7	19	34	22	200	0.6	128	7.6	
21	15	1	1.3	54	5.6	16	16	17	167	0.7	118	7.3	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	15	1	108	139	4.8	2.1	104	9.4	3.7	153	189		
21	15	1	95	139	4.8	2.3	100	9.2	3.9	125	179		
Subject 16 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)	
-7	16	1	0.95	47	5.5	22	22	13	238	0.6	58	7.1	
21	16	1	0.8	37	3.9	16	16	10	259	0.7	47	6.7	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	16	1	102	143	4.6	1.7	105	9.8	2.8	109	220		
21	16	1	98	144	5.4	1.9	103	9.6	2.6	96	207		

Equival[®] capsules

Subject 17 - centre 1

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	17	1	0.8	32	5.1	16	19	37	238	0.8	133	7
21	17	1	0.9	28	5.1	12	18	29	232	1.8	161	6.9
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	17	1	101	138	4.6	2.1	104	10	2.4	68	200	
21	17	1	86	141	4.5	2.3	101	10.2	2.4	87	200	

Subject 18 - centre 1

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	18	1	1.21	33	6.1	18	19	34	230	0.9	70	7
21	18	1	1.19	32	6	18	18	33	230	0.9	66	7
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	18	1	106	137	4.9	2.1	105	10	2.6	115	205	
21	18	1	110.8	137	4.8	2.1	103	10	2.4	110	200	

Equoral® capsules

Subject 19 - centre 1

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	19	1	1	30	5.1	19	21	34	226	0.9	60	6.8
21	19	1	1	33	5.1	20	21	34	226	0.8	60	6.8

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)

-7	19	1	91	135	4.6	1.7	104	11	3.1	180	228
21	19	1	93	135	4.5	1.8	105	11	3.2	170	231

Subject 20 - centre 1

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	20	1	1	34	4.6	12	17	12	238	0.8	64	6.1
21	20	1	1.05	35	5.3	15	23	14	220	0.8	40	6.4

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)

-7	20	1	96	137	3.9	1.7	104	9	2.6	180	234
21	20	1	99	134	3.9	2	105	9	2.6	160	240

Equoral® capsules

Subject 21 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	21	1	1.5	33	8	14	21	13	222	0.8	40	6.6	
21	21	1	1.5	33	8	14	22	13	221	0.8	41	6.6	
Subject 22 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	21	1	100	130	4	2	104	10	2.6	181	241		
21	21	1	102	136	4	2	105	10	2.6	170	235		

Subject 22 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	22	1	1.18	36	6.4	16	29	16	229	0.9	66	6.6	
21	22	1	1.2	35	6.3	15	28	17	272	0.9	65	6.8	
Subject 23 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	22	1	104	138	4.8	1.9	106	9	2.6	190	248		
21	22	1	100	135	4.5	2	105	9.1	2.6	198	239		

Equoral® capsules

Subject 23 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	23	1	1.47	36	6	31	21	14	230	0.9	80	6.8	
21	23	1	1.38	34	6.1	33	25	15	220	0.9	82	6.7	
Subject 24 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	23	1	98	140	4.2	2.1	106	9	2.3	189	260		
21	23	1	95	140	4.2	2.1	108	9	2.6	191	253		
Subject 24 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	24	1	0.8	28	5.1	30	19	15	278	0.8	55	6.8	
21	24	1	0.8	30	5.1	31	19	14	286	0.8	66	6.7	
Subject 24 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	24	1	92	140	4.1	2	105	8.6	2.4	160	195		
21	24	1	90	140	4.2	2	105	8.8	2.2	165	190		

Equorex® capsules

Subject 25 - centre 1		Centre No.	Subject No.	Day	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
		1	25	-7	1.3	38	6.1	28	23	12	239	0.9	66	6.8
		1	25	21	1.33	36	6.2	25	20	14	139	0.9	63	6.8
		Centre No.	Subject No.	Day	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
		1	25	-7	101	142	4.3	2	105	8.8	3	189	240	
		1	25	21	103	150	3.4	2	106	8.4	23	195	235	

Subject 26 - centre 1		Centre No.	Subject No.	Day	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
		1	26	-7	1.45	38	6.2	33	19	14	220	0.8	46	6.8
		1	26	21	1.45	38	6.1	31	20	14	219	0.8	36	6.7
		Centre No.	Subject No.	Day	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
		1	26	-7	110	145	4	2	106	8.5	23	230	240	
		1	26	21	111	160	4.1	2	105	9.5	8	210	243	

Equoral® capsules

Subject 27 - centre 1												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	27	1	0.6	30	5.4	24	18	12	217	0.8	38	6.8
21	27	1	0.8	29	5.2	25	18	18	233	0.8	44	6.8
Subject 28 - centre 1												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	27	1	90	170	4	2	105	9.4	154	130	210	
21	27	1	95	168	5.4	2	105	9.2	208	170	215	

Subject 28 - centre 1												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	28	1	1.3	40	6.4	28	19	14	250	0.8	66	6.7
21	28	1	1.3	41	6.6	28	19	14	210	0.8	68	6.8
Subject 29 - centre 1												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	28	1	110	160	4.1	2.8	106	8.8	4	140	190	
21	28	1	110	160	4.2	2	105	9	5	145	190	

Equoral[®] capsules

Subject 29 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	29	1	1.47	38	6.2	29	23	14	218	0.8	80	6.7	
21	29	1	1.47	37	6.1	33	24	13	228	0.8	71	6.8	
Subject 30 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	29	1	100	145	4.1	2	105	9.1	2	200	260		
21	29	1	95	146	4	2	105	9	2	182	244		

Subject 30 - centre 1													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	30	1	0.85	28	5.1	28	21	12	219	0.8	66	6.8	
21	30	1	0.85	29	5.2	28	21	11	216	0.7	67	6.7	
Subject 31 - centre 1													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	30	1	90	146	4.1	2.1	105	9	2	160	200		
21	30	1	90	144	4.2	2.1	104	9	2	160	200		

Equoral[®] capsules

Subject 1 - centre 3		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	1	3	1.16	14	6.3	21	15	37	412	1.09	ND	6.73
21	1	3	1.1	16	5.8	17	22	32	421	0.4	106	6.9

Subject 2 - centre 3		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
Day	Subject No.										
-7	1	3	82	144	4	2	108	10.5	3.46	129	181
21	1	3	82	144	4	1.9	106	10.2	3.8	116	196

Subject 2 - centre 3		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	2	3	1.15	15	4.9	23	38	40	445	0.5	10	7
21	2	3	1.1	16	5.2	23	38	42	428	0.4	10	7.1

Subject 3 - centre 3		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
Day	Subject No.										
-7	2	3	93	137	3.8	1.7	104	9.9	3.1	360	199
21	2	3	88	138	4.1	1.9	105	9.6	3.1	282	186

Equoral[®] capsules

Subject 3 - centre 3		Centre No.	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.										
-7	3	3	17	6.2	18	15	13	210	2.46	104	7.08
21	3	3	17	6.2	18	15	13	216	2.33	ND	7
Subject 3 - centre 3		Centre No.	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.										
-7	3	3	143	4.3	1.9	104	10	3.16	87	117	
21	3	3	143	4.3	1.8	105	9.4	3.16	87	200	

Subject 4 - centre 3		Centre No.	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.										
-7	4	3	35	8.1	19	7	15	277	1.7	40	7.35
21	4	3	32	8.3	13	10	13	308	1.3	40	7.4
Subject 4 - centre 3		Centre No.	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.										
-7	4	3	140	5.3	1.7	99	9.7	4.49	143	179	
21	4	3	141	3.8	1.8	103	10.1	4.2	115	167	

Equoral[®] capsules

Subject 5 - centre 3												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	5	3	0.9	18	7	23	27	30	238	0.8	ND	7.47
21	5	3	0.9	14	38	22	21	32	286	1.8	ND	8.2

Total												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	5	3	79	136	3.3	2.2	101	10.1	3.4	290	232	
21	5	3	94	144	3.3	1.8	101	10.4	3	258	207	

Subject 6 - centre 3												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	6	3	1.2	32	5.1	22	18	30	175	1	79	7.3
21	6	3	1.2	23	5.1	29	22	31	189	0.7	80	6.6

Total												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	6	3	88	139	4.9	2	108	10.1	4.3	112	189	
21	6	3	101	125	4.7	1.7	103	9.5	3.8	113	157	

Equoral[®] capsules

Subject 7 - centre 3													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	7	3	1.1	21	6.1	17	14	15	144	0.9	86	7.6	
21	7	3	1.1	26	6.8	15	13	17	165	1.2	87	8.8	
Subject 8 - centre 3													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	7	3	74	141	4.1	1.7	107	9.9	3.35	136	193		
21	7	3	95	139	4.2	1.8	102	10.1	3.13	165	194		

Subject 8 - centre 3													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	8	3	1	15	6.5	11	16	42	152	0.7	78	7.6	
21	8	3	1	14	6.5	14	16	58	172	1.1	98	7.4	
Subject 9 - centre 3													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	8	3	94	142	3.9	1.9	110	10.1	3.3	208	216		
21	8	3	92	142	4.2	2	108	10.1	3.2	123	186		

Equoral[®] capsules

Subject 9 - centre 3												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	9	3	138	15	7.4	19	15	52	142	2.4	96	7.6
21	9	3	1	11	8	21	22	88	116	2.8	121	7.1
Subject 10 - centre 3												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	9	3	93	143	4.3	1.9	104	9.7	5.4	113	120	
21	9	3	101	143	4.1	2	109	8.6	2.5	128	188	

Subject 10 - centre 3												
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	10	3	1.8	28	8.8	14	15	52	145	1.6	182	7
21	10	3	1.9	28	7.9	19	18	45	121	1.8	106	7.1
Subject 10 - centre 3												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	10	3	100	140	4.3	1.9	110	10.3	5.8	110	183	
21	10	3	98	138	3.9	1.8	108	9.7	5.3	109	125	

Equivocal capsules

Subject 1 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	1	4	1.3	13	ND	31	32	30	133	0.43	ND	8.2
21	1	4	1.17	13	7	29	22	31	93	0.68	78	7.5
Total												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	cholesterol (mg/dL)	
-7	1	4	88	141	3.8	2.37	109	10.4	4.3	134	147	
21	1	4	96	138	4	2.36	106	9.4	4.2	93	127	

Subject 2 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	2	4	0.82	10	5.6	18	18	25	68	0.38	111	8
21	2	4	0.81	13	5.3	11	16	14	80	0.43	67	7.6
Total												
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	cholesterol (mg/dL)	
-7	2	4	109	139	3.3	2.39	103	11.3	5.3	96	183	
21	2	4	104	136	3.8	2.03	106	10.4	1.8	145	204	

Equival[®] capsules

Subject 3 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	3	4	1.27	11	0.8	20	21	22	82	1.23	134	7.7
21	3	4	1.14	13	0.8	17	15	20	77	1.49	168	7.6
		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	3	4	103	142	3.8	1.99	108	10.2	2.4	96	183	
21	3	4	77	131	3.6	2.19	103	9.7	4.3	498	173	

Subject 4 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	4	4	0.99	18	1.1	21	13	83	116	0.59	116	7.6
21	4	4	0.96	20	1.0	21	93	45	69	0.69	107	7.9
		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	4	4	107	139	4.5	1.95	110	9.5	2.8	263	192	
21	4	4	89	137	3.5	2.01	110	9.5	3.9	347	187	

Equoral[®] capsules

Subject 5 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	5	4	1.06	23	ND	13	19	27	79	0.67	ND	7.4
21	5	4	1.17	30	93	18	20	28	85	0.41	109	7.8
		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	5	4	95	142	3.9	2.58	107	10.3	8	209	239	
21	5	4	90	142	4.2	2.38	108	10.4	98	318	208	

Subject 6 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	6	4	1.13	21	127	27	40	30	89	0.83	63	6.9
21	6	4	0.97	18	83	17	26	26	83	1.1	103	7.5
		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	6	4	81	142	4.1	1.72	110	9.4	3.4	107	163	
21	6	4	96	145	4.4	1.84	110	9.9	4	124	170	

Equoraf® capsules

Subject 7 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	7	4	1.1	14	8.6	9	17	16	131	1.08	80	7.3
21	7	4	1.09	13	6.6	9	18	17	141	0.98	65	7.7
Subject 8 - centre 4		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	7	4	79	142	4	1.78	109	9.5	3.3	141	118	
21	7	4	81	142	4.3	1.7	108	9.6	3.9	167	128	

Subject 8 - centre 4		Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
Day	Subject No.											
-7	8	4	2.02	25	8.1	193	89	10	42	0.49	152	6.7
21	8	4	1.92	18	7.3	209	13.7	145	61	0.79	102	7.4
Subject 9 - centre 4		Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
Day	Subject No.											
-7	8	4	83	141	4.1	2.2	108	9.5	4	155	166	
21	8	4	82	145	4.4	1.98	107	10.3	4.5	180	202	

Equoral[®] capsules

Subject 9 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	9	4	0.9	18	8.8	8	15	14	69	0.64	83	6.7
21	9	4	1.03	20	8.8	12	16	13	68	0.88	82	7.3
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	9	4	122	138	4.5	1.84	106	9.8	3.9	148	171	
21	9	4	100	144	4.4	2.06	116	10.4	4.6	206	200	

Subject 10 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	10	4	0.94	13	8.6	22	22	19	116	0.99	128	7.4
21	10	4	1.19	15	8.8	23	19	26	122	0.61	101	7.4
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	10	4	84	146	4.7	2.01	108	10.3	3.1	928	247	
21	10	4	88	143	4.1	2.51	108	10.1	4	155	268	

Equoral[®] capsules

Subject 11 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	11	4	1.44	24	6.6	25	27	44	99	0.84	95	6.9
21	11	4	1.35	27	6.6	23	24	52	117	0.68	149	7.1

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	11	4	146	142	3.9	2.41	110	9.5	4.9	320	252
21	11	4	176	141	4.4	2.4	112	9.4	5.4	335	250

Subject 12 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	12	4	1.47	25	6.3	10	17	16	123	0.47	93	6.7
21	12	4	1.58	33	6.2	16	14	18	111	0.23	98	6.7

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	12	4	90	142	4.3	2.18	112	9.5	4.7	66	145
21	12	4	86	142	5.3	2.2	115	9.6	5.6	85	132

Equoral® capsules

Subject 13 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	13	4	1.57	38	9.5	12	17	15	88	1.09	125	7
21	13	4	1.3	25	9.3	10	18	13	88	1.04	109	6.2

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	13	4	85	139	4.9	2.35	111	9.8	5.3	262	246
21	13	4	84	141	4	2.17	111	9.5	4.3	122	237

Subject 14 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	14	4	1.55	27	8.6	25	24	88	101	0.31	71	8
21	14	4	1.58	25	8.1	14	16	89	92	0.3	87	7.5

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	14	4	135	141	5.3	2.69	117	8.9	88	615	234
21	14	4	88	140	4.6	2.3	121	8.4	4.8	403	201

Equoral[®] capsules

Subject 15 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	15	4	0.83	14	3.8	241	214	35	102	0.55	34	7.5
21	15	4	1.38	12	3.3	208	127	44	92	0.59	49	7.3
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	15	4	76	137	4.9	1.93	109	9.6	3.7	84	163	
21	15	4	78	138	4.4	1.71	111	9.2	3.7	63	171	

Subject 16 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	16	4	1.63	17	7	20	21	138	115	1.44	144	6.7
21	16	4	1.62	8	3.4	13	25	162	111	1.25	142	6.4
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)	
-7	16	4	71	135	3.8	2.13	101	8.7	3.7	155	213	
21	16	4	97	133	3.1	1.7	101	9.2	3.8	127	186	

Equoral[®] capsules

Subject 17 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	17	4	1.39	24	3.2	10	19	15	83	0.68	113	8.1
21	17	4	1.29	21	3.3	12	20	15	88	0.85	86	8.6

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	17	4	85	149	4.9	2.69	113	12.2	534	314	288
21	17	4	86	139	4.1	1.93	111	10.2	3.8	285	299

Subject 18 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	18	4	1.25	15	6.8	9	19	35	82	0.52	127	8.1
21	18	4	1.58	22	9.1	33	36	68	88	0.83	69	8.3

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	18	4	79	144	4.4	2.69	115	11.9	82	169	156
21	18	4	81	140	4.1	1.94	113	9.5	531	164	163

Equoral[®] capsules

Subject 19 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	19	4	1.09	24	7.3	38	38	60	96	0.78	112	6.9
21	19	4	1.21	20	3.3	46	30	45	79	1.05	61	7.2

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Calcium (mg/dL)	Chloride (mmol/L)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	19	4	115	140	3.8	2.47	9.1	108	4.7	133	217
21	19	4	124	135	3.7	1.82	9.8	106	4.3	161	198

Subject 20 - centre 4

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	20	4	1.04	20	9.3	23	18	15	97	0.57	211	8
21	20	4	1.55	27	10.2	25	36	12	76	0.72	163	8.9

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Calcium (mg/dL)	Chloride (mmol/L)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	20	4	74	146	4.2	2.56	10.9	117	88	131	224
21	20	4	73	144	4.2	2.17	9.5	119	53	115	206

Equoral® capsules

Subject 1 - centre 5													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	1	5	1.2	23	8.8	15	19	27	76	0.65	110	7.4	
21	1	5	1.17	26	8	18	20	28	85	0.66	109	7.8	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	1	5	95	142	3.9	2.28	106	10.4	5	207	229		
21	1	5	91	142	4.2	2.38	106	10.4	5.2	222	208		

Subject 2 - centre 5													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	2	5	1.43	14	7.9	30	29	31	88	0.41	145	8.2	
21	2	5	1.38	15	8.8	31	32	30	76	0.51	139	8.2	
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)		
-7	2	5	88	141	3.8	2.11	109	10.4	4.4	135	149		
21	2	5	84	141	4.3	2.01	110	10.4	4.2	134	147		

Equoral® capsules

Subject 3 - centre 5													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	3	5	1.05	16	5.5	18	21	25	68	0.49	111	8.1	
21	3	5	1.02	17	5.6	16	19	28	68	0.46	116	7.9	
Total													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)		cholesterol (mg/dL)	
-7	3	5	101	139	3.3	2.43	104	11	3.8	93		159	
21	3	5	102	140	3.9	2.39	106	11.3	3.9	104		156	

Subject 4 - centre 5													
Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)	
-7	4	5	1.38	13	7.1	21	23	22	69	1.13	125	7.7	
21	4	5	1.28	12	8.3	17	24	20	71	1.23	155	7.6	
Total													
Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)		cholesterol (mg/dL)	
-7	4	5	100	142	3.3	1.99	107	10.2	2.8	143		183	
21	4	5	88	140	3.9	2.19	108	10.3	3	134		173	

Equoral[®] capsules

Subject 5 - centre 5

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	5	5	1.09	19	6.6	33	30	33	106	0.67	116	7.6
21	5	5	1.07	20	5.4	33	33	52	102	0.59	117	6.9

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	5	5	97	139	4.5	1.89	110	9.8	2.8	233	153
21	5	5	90	140	4.7	1.95	107	9.9	2.8	211	149

Subject 6 - centre 5

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	6	5	1.43	18	8.2	11	18	18	61	0.64	98	6.7
21	6	5	1.42	20	8	13	16	19	68	0.78	88	7.3

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	6	5	113	138	4.5	2.01	109	9.8	3.9	148	171
21	6	5	109	144	4.4	2.06	106	10.1	4.3	153	188

Equoral capsules

Subject 7 - centre 5

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	7	5	1.34	21	8.8	9	17	16	101	1.09	156	7.3
21	7	5	1.34	17	8.8	11	18	17	92	1.03	175	7.2

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	7	5	87	142	4	1.78	107	10.1	3.2	174	118
21	7	5	81	142	4.3	1.88	104	9.9	3.3	169	128

Subject 8 - centre 5

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin	Amylase (U/L)	Protein (mg/dL)
-7	8	5	1.61	24	7.3	22	43	65	43	0.61	133	6.7
21	8	5	1.63	21	7.3	26	40	66	48	0.71	102	6.9

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	8	5	73	141	4.1	1.76	109	10.5	3.4	184	187
21	8	5	71	145	4.4	1.98	109	10.3	3.9	180	202

Equoral[®] capsules

Subject 9 - centre 5

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	9	5	1.23	21	5.6	27	40	38	49	0.83	99	6.9
21	9	5	1.19	24	5	25	37	38	44	1	103	7.3

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	9	5	83	142	4.1	1.92	111	9.7	3.4	124	163
21	9	5	86	145	4.4	1.84	111	9.9	3.4	132	170

Subject 10 - centre 5

Day	Subject No.	Centre No.	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	ALAT (U/L)	ASAT (U/L)	GMT (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	Amylase (U/L)	Protein (mg/dL)
-7	10	5	1.54	22	7.5	28	24	45	56	0.73	173	6.9
21	10	5	1.55	27	6.9	23	24	41	44	0.68	149	7.1

Day	Subject No.	Centre No.	Glucose (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mg/dL)	Chloride (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
-7	10	5	110	144	3.8	2.34	112	9.6	4.2	266	231
21	10	5	116	141	4.4	2.22	106	9.7	4.1	219	219

Value abnormal value

Value clinically significant abnormal value

Equoral® capsules

16.2.8.3 URINALYSIS

Subject 1 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	301
21	5	0	0	0	0	0	347

Subject 2 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	209
21	5	0	0	0	0	0	119

Subject 3 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	163
21	5	0	0	0	0	0	187

Subject 4 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	48
21	5	0	0	0	0	0	57

Subject 5 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	0	0	0	0	0	193
21	5	0	0	0	0	0	159

Equoral[®] capsules

Subject 6 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	181
21	5	0	0	0	0	0	198

Subject 7 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,5	0	0	0	0	0	27
21	6,5	0	0	0	0	0	14

Subject 8 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	0	0	0	0	0	70
21	5	0					

Subject 9 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	319
21	5	0	0	0	0	0	250

Subject 10 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	0	0	0	0	0	60
21	6	0	0	0	0	0	67

Subject 11 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,5	0	0	0	0	0	305
21	6,5	0	0	0	0	0	216

Equoral[®] capsules

Subject 12 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	24
21	5	ND	ND	ND	ND	ND	ND

Subject 13 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	0	0	0	0	0	142
21	6,5	0	0	0	0	0	183

Subject 14 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	98
21	6	0	0	0	0	0	77

Subject 15 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	25	0	0	0	0	92
21	5	25	0	0	0	0	211

Subject 16 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	225
21	5	0	0	0	0	0	240

Subject 17 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,5	0	0	0	0	0	318
21	6,5	0	ND	ND	ND	ND	ND

Equoral® capsules

Subject 18 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,6	0	0	0	0	0	311
21	ND	0	0	0	0	0	120

Subject 19 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	300
21	6,1	ND	ND	ND	ND	ND	300

Subject 20 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6,2	ND	ND	ND	ND	ND	300

Subject 21 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,3	ND	ND	ND	ND	ND	300
21	6,1	ND	ND	ND	ND	ND	300

Subject 22 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,2	ND	ND	ND	ND	ND	ND
21	6,1	ND	ND	ND	ND	ND	ND

Subject 23 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,2	ND	ND	ND	ND	ND	ND
21	6,1	ND	ND	ND	ND	ND	ND

Equoral® capsules

Subject 24 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,2	ND	ND	ND	ND	ND	ND
21	6,3	ND	ND	ND	ND	ND	ND

Subject 25 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,1	ND	ND	ND	ND	ND	ND
21	6,1	ND	ND	ND	ND	ND	ND

Subject 26 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,1	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 27 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6,1	ND	ND	ND	ND	ND	ND

Subject 28 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 29 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Equoral® capsules

Subject 30 - centre 1

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,1	ND	ND	ND	ND	ND	ND
21	6,1	ND	ND	ND	ND	ND	ND

Subject 1 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	ND	ND	ND	ND	ND	ND
21	5,5	ND	ND	ND	ND	ND	98

Subject 2 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	300	ND	ND	ND	ND	82
21	5,5	300	ND	ND	ND	ND	78

Subject 3 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	74
21	5	ND	ND	ND	ND	ND	ND

Subject 4 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	127
21	6	ND	ND	ND	ND	ND	78

Subject 5 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	104
21	5	ND	ND	ND	ND	ND	ND

Equanal® capsules

Subject 6 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	247
21	5	0	0	0	0	0	163

Subject 7 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	189
21	5	0	0	0	0	0	97

Subject 8 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	89
21	5	0	0	0	0	0	127

Subject 9 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	128
21	5	0	0	0	0	0	126

Subject 10 - centre 3

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	0	0	0	0	0	108
21	5	0	0	0	0	0	126

Subject 1 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

53/BQ/01/PTK (IVAX Pharmaceuticals s.r.l.) ----- Clinical Study Report

Final version 21.5.2004

Equival[®] capsules

Subject 2 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 3 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 4 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	Tracc	ND	ND	ND	ND	ND
21	6	10	ND	ND	ND	ND	ND

Subject 5 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	5	ND	ND	ND	ND	ND	ND

Subject 6 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	5	ND	ND	ND	ND	ND	ND

Subject 7 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	5	ND	ND	ND	ND	ND	ND

Equival[®] capsules

Subject 8 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 9 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	5	ND	ND	ND	ND	ND	ND

Subject 10 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	Trace	ND	ND	ND

Subject 11 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5.5	Trace	ND	ND	ND	ND	ND
21	5.5	ND	ND	ND	ND	ND	ND

Subject 12 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	ND	ND	Trace	ND	ND	ND
21	6	ND	ND	Trace	ND	ND	ND

Subject 13 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Equoral® capsules

Subject 14 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5,5	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 15 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6,5	ND	ND	ND	ND	ND	ND

Subject 16 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6,5	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 17 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5,5	ND	ND	ND	ND	ND	ND
21	5	ND	ND	ND	ND	ND	ND

Subject 18 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	ND	ND	ND

Subject 19 - centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6,5	ND	ND	ND	ND	ND	ND

Equorel® capsules

Subject 10 – centre 4

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	5	40	ND	ND	ND	ND	ND

Subject 1 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5,7	ND	ND	ND	ND	ND	ND
21	5,5	ND	ND	ND	ND	0	ND

Subject 2 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5,5	ND	ND	ND	0	ND	ND
21	5,5	ND	ND	ND	0	ND	ND

Subject 3 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	ND	ND	ND	0	ND	ND
21	5	ND	ND	ND	0	ND	ND

Subject 4 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	ND	ND	ND	ND	ND	ND
21	5,5	ND	ND	ND	0	ND	ND

Subject 5 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	ND	ND	ND	0	ND	ND
21	5	ND	ND	ND	0	ND	ND

Equoral® capsules

Subject 6 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	0	ND	ND
21	6.5	ND	ND	ND	0	ND	ND

Subject 7 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	6	ND	ND	ND	0	ND	ND

Subject 8 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	0	ND	ND
21	6.5	ND	ND	ND	0	ND	ND

Subject 9 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	6	ND	ND	ND	ND	ND	ND
21	5	ND	ND	ND	0	ND	ND

Subject 10 – centre 5

Day	pH	Protein	Glucose	Haemoglobin	Bile	Acetone	Amylase (U/L)
-7	5	ND	ND	ND	0	ND	ND
21	5	ND	ND	ND	0	ND	ND

Value abnormal value

Equoral® capsules

16. Appendices

16.2 Patient Data Listings

16.2.9 Listing of Individual Vital Signs Measurements (by Patient)

Equival[®] capsules

16.2.9 VITAL SIGNS LISTINGS (EACH PATIENT)

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
1	1	-7	46	11	76	140	95	37.2	69.6
		0	46	11	78	140	96	37.2	69.6
		13	46	11	63	130	80	37	69
		14	46	11	63	136	80	36.8	69
		15	46	11	68	140	80	36.8	70
		18	46	11	76	120	90	37	70
		21	46	11	88	130	95	37.2	69.5
		27	46	11	68	140	90	37	69.5
		28	46	11	68	140	90	37	69.5
		29	46	11	75	120	70	37	68.5
		35	46	11	80	122	80	36.9	68.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
2	1	-7	34	21	84	120	70	36.5	61
		0	34	21	80	100	60	36.8	60.5
		13	34	21	80	130	70	36.5	60.3
		14	34	21	75	135	60	37.0	60
		15	34	21	65	110	60	37	60.2
		18	34	21	72	90	50	37	60
		21	34	21	80	102	72	36.5	60
		27	34	21	80	100	70	37	60.5
		28	34	21	80	110	60	36.8	60
		29	34	21	75	100	60	36.5	60.2
		35	34	21	80	88	60	37	61.5

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
3	1	-7	36	31	76	150	78	37.2	123
		0	36	31	100	140	90	36.6	124.5
		13	36	31	70	135	85	37	123.5
		24	36	31	68	160	80	37.0	123.5
		15	36	31	80	160	80	36.8	124.5
		18	36	31	80	140	80	36.8	122.5
		21	36	31	84	120	50	36.8	122
		27	36	31	68	140	70	37.5	123
		28	36	31	68	140	70	37	123.5
		29	36	31	80	140	60	37.3	123
		35	36	31	84	130	72	36.9	123.2

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
4	1	-7	67	41	72	140	76	36.6	56.5
		0	67	41	76	140	86	35.8	56.5
		13	67	41	60	120	75	36.2	58
		14	67	41	56	180	70	37.0	58
		15	67	41	60	150	65	36.8	58.2
		18	67	41	72	148	70	36.4	57
		21	67	41	84	140	70	36.6	57
		27	67	41	60	140	80	36.4	58
		28	67	41	64	130	80	36.8	58
		29	67	41	60	125	70	37	58.2
		35	67	41	64	130	60	37	58.5

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
5	1	-7	62	51	88	132	88	36.5	76
		0	62	51	72	140	90	35.8	66
		13	62	51	64	140	90	37.0	66.5
		14	62	51	60	140	90	37.0	66
		15	62	51	70	140	85	36.8	66
		18	62	51	68	140	90	36.6	66.5
		21	62	51	78	140	90	36.8	67
		27	62	51	68	120	80	36.8	68
		28	62	51	68	120	80	37.0	68
		29	62	51	65	130	65	37.0	67.5
		35	62	51	70	120	70	36.8	67.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
6	1	-7	47	61	92	112	66	36.5	54
		0	47	61	80	120	76	36.8	55
		13	47	61	80	140	70	36.4	55.5
		14	47	61	84	140	60	36.0	55
		15	47	61	80	140	60	36.2	55.5
		18	47	61	80	90	60	36.4	55.5
		21	47	61	80	112	70	36.2	56
		27	47	61	80	130	70	37.0	56.5
		28	47	61	75	120	60	36.6	55.5
		29	47	61	80	110	60	37.0	56
		35	47	61	80	100	60	37.0	56

Equival® capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
7	1	-7	25	71	80	110	72	36.6	51
		0	25	71	68	106	70	36.6	51.5
		13	25	71	70	120	80	36.8	51
		14	25	71	76	130	90	36.8	51
		15	25	71	85	100	60	37	51
		18	25	71	80	92	50	36.7	51
		21	25	71	80	102	60	36.5	51
		27	25	71	80	110	70	36.4	51.5
		28	25	71	80	100	84	36	51.5
		29	25	71	70	110	60	36.4	51.7
		35	25	71	72	100	60	36.6	51.7

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
8	1	-7	35	81	80	120	78	36.5	66
		0	35	81	68	122	80	36	66.5
		13	35	81	80	112	80	36.6	66.5
		14	35	81	70	110	70	36.8	66.2
		15	35	81	75	115	70	36.8	66
		18	35	81	80	110	70	37	66
		21	35	81	68	118	80	37	67
		27	35	81	64	120	70	36.6	66
		28	35	81	60	110	60	37	66.2
		29	35	81	80	120	80	36.6	66.5
		35	35	81	84	120	90	37	67

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
9	1	-7	25	91	72	110	80	36.6	53
		0	25	91	72	100	62	36	53.2
		13	25	91	70	100	80	35	52
		14	25	91	80	110	82	35.0	52
		15	25	91	83	90	50	35.6	52.2
		18	25	91	100	92	40	36	52
		21	25	91	72	102	70	36	53
		27	25	91	70	100	50	36.2	52.5
		28	25	91	68	106	60	36.2	53
		29	25	91	65	100	50	36	53
		35	25	91	76	100	60	36	53

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
10	1	-7	37	101	97	180	106	37.4	54.5
		0	37	101	90	140	100	37	53.2
		13	37	101	70	140	100	37	55
		14	37	101	68	140	100	37.0	55
		15	37	101	68	135	90	37.2	55
		18	37	101	76	120	80	37.2	56
		21	37	101	80	160	100	36.8	56
		27	37	101	76	140	95	37.3	55.5
		28	37	101	72	124	80	37	56
		29	37	101	76	150	90	37	57
		35	37	101	80	160	100	37.2	57

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
11	1	-7	29	111	100	132	90	37	78
		0	29	111	92	120	84	36.8	77.5
		13	29	111	80	130	85	37.2	77
		14	29	111	72	120	90	36.4	77.5
		15	29	111	75	135	80	37.2	77.5
		18	29	111	80	130	80	37	77.8
		21	29	111	ND	ND	ND	ND	ND
		27	29	111	70	120	70	37	77
		28	29	111	72	110	60	36.2	77
		29	29	111	70	100	70	36.5	77.5
		35	29	111	72	130	90	36.5	77.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
12	1	-7	56	121	68	120	70	36	77
		0	56	121	56	100	62	36.8	77.5
		13	56	121	68	120	80	36.6	77
		14	56	121	60	126	80	36.8	77
		15	56	121	76	110	70	37	77
		18	56	121	64	110	70	36.6	76
		21	56	121	72	124	80	37	75.5
		27	56	121	70	120	65	37	75.5
		28	56	121	80	120	60	37.5	75.5
		29	56	121	70	115	75	37	75.5
		35	56	121	80	120	80	37	76.5

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
13	1	-7	33	131	98	110	60	36.8	70.5
		0	33	131	72	124	60	36.6	69
		13	33	131	70	110	80	37	68.5
		14	33	131	80	140	70	36.8	68.2
		15	33	131	70	115	40	37	69
		18	33	131	80	102	50	36.8	69.5
		21	33	131	80	110	70	37	69
		27	33	131	60	105	50	36.8	70.5
		28	33	131	86	100	60	37	70.5
		29	33	131	70	110	70	36.8	69
		35	33	131	80	120	80	37	69.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
14	1	-7	29	141	98	92	60	36.4	53
		0	29	141	70	100	70	36.4	53
		13	29	141	80	90	50	36.2	53.5
		14	29	141	84	90	40	36.4	53.2
		15	29	141	80	95	50	37	53.2
		18	29	141	72	88	42	36	53
		21	29	141	80	106	50	36.8	53.5
		27	29	141	70	90	40	36.2	53.2
		28	29	141	64	90	60	36	53.5
		29	29	141	70	90	60	37	53.5
		35	29	141	93	110	70	36.8	54.5

Eq. 111 capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
15	1	-7	54	151	54	170	82	36.2	62.5
		0	54	151	54	170	80	36	63
		13	54	151	80	160	70	36.4	62
		14	54	151	80	160	80	36.8	62.2
		15	54	151	70	130	60	36.8	62.4
		18	54	151	80	140	70	37	62.5
		21	54	151	80	153	80	36	63
		27	54	151	60	100	60	36.4	62.2
		28	54	151	68	110	70	37	62.5
		29	54	151	70	93	60	36.8	62
		35	54	151	72	158	70	37	61

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
16	1	-7	43	161	58	108	70	36.6	81
		0	43	161	80	108	80	37	80.5
		13	43	161	70	120	90	36.8	80.5
		14	43	161	70	120	90	36.8	80.5
		15	43	161	80	110	70	37	80.5
		18	43	161	62	110	74	37	79.5
		21	43	161	80	130	76	37	80.5
		27	43	161	68	100	80	37	80.5
		28	43	161	72	110	80	36.8	80.5
		29	43	161	76	100	70	36.8	80.5
		35	43	161	80	110	80	37	81

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
17	1	-7	39	171	84	120	80	36	64
		0	39	171	100	120	80	36.8	64
		13	39	171	100	122	85	36.4	64
		14	39	171	84	130	100	36.7	64
		15	39	171	100	125	85	36.7	64
		18	39	171	100	110	80	36.8	63
		21	39	171	96	130	76	36.7	64
		27	39	171	90	120	80	36.6	64
		28	39	171	88	130	80	36.7	64
		29	39	171	80	110	84	36.7	64
		35	39	171	76	100	80	36.7	63

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
18	1	-7	45	181	86	120	80	36	77.5
		0	45	181	86	120	80	36.5	77
		13	45	181	86	118	80	36.5	77.5
		14	45	181	86	118	80	36.2	77
		15	45	181	90	120	88	36.6	77
		18	45	181	88	120	85	36.5	77.2
		21	45	181	90	116	82	36.5	77.5
		27	45	181	90	120	80	36.4	77.5
		28	45	181	90	115	80	36.5	77.5
		29	45	181	86	110	85	36.5	77.5
		35	45	181	90	120	85	36.4	77.3

Equora[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
19	1	-7	30	191	90	130	101	36.4	75.2
		0	30	191	93	128	100	36.5	75.3
		13	30	191	88	122	98	36.5	75.5
		14	30	191	90	120	98	36.5	75.5
		15	30	191	90	125	103	36.5	75.3
		16	30	191	93	130	102	36.4	75.5
		21	30	191	90	125	100	36.4	75.5
		27	30	191	95	130	104	36.4	75.5
		28	30	191	90	130	105	36.5	75.5
		29	30	191	92	128	100	36.3	75.4
		35	30	191	90	128	98	36.6	75.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
20	1	-7	34	201	88	120	80	36.6	64.6
		0	34	201	88	120	80	36.7	64.5
		13	34	201	85	124	85	36.5	64.2
		14	34	201	80	120	82	36.4	64.2
		15	34	201	80	120	81	36.5	64.3
		18	34	201	80	120	80	36.5	64.6
		21	34	201	80	120	85	36.3	64.6
		27	34	201	80	120	83	36.6	64.7
		28	34	201	85	125	90	36.5	64.7
		29	34	201	85	125	82	36.6	64.6
		35	34	201	85	125	82	36.6	64.6

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
21	1	-7	37	211	89	118	80	36.2	68.3
		0	37	211	87	122	86	36.4	58.5
		13	37	211	80	122	85	36.4	58.2
		14	37	211	85	126	88	36.3	58.5
		15	37	211	88	125	89	36.5	58.5
		18	37	211	89	125	86	36.5	58.5
		21	37	211	85	125	86	36.5	58.4
		27	37	211	88	126	88	36.7	58.4
		28	37	211	85	125	88	36.5	58.4
		29	37	211	90	126	86	36.6	58.5
		35	37	211	82	122	80	36.5	58.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
22	1	-7	27	221	100	135	95	36.5	79.5
		0	27	221	98	130	90	36.4	74.8
		13	27	221	96	130	100	36.5	79.8
		14	27	221	101	130	98	36.5	79.5
		15	27	221	98	133	100	36.2	79.6
		18	27	221	100	130	101	36.4	79.6
		21	27	221	98	128	95	36.3	79.2
		27	27	221	96	128	95	36.5	79.8
		28	27	221	95	129	100	36.5	79.5
		29	27	221	98	130	101	36.4	79.4
		35	27	221	100	132	101	36.5	79.7

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
23	1	-7	35	231	88	120	80	36.5	76.3
		0	35	231	88	122	80	36.3	76.3
		13	35	231	90	125	80	36.4	76.5
		14	35	231	ND	ND	ND	ND	ND
		15	35	231	84	120	82	36.5	76.5
		18	35	231	84	126	84	36.3	76.4
		21	35	231	84	123	83	36.5	76.6
		27	35	231	84	128	80	36.5	76.8
		28	35	231	85	126	89	36.5	76.3
		29	35	231	ND	ND	ND	ND	ND
		35	35	231	86	125	80	36.5	76.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
24	1	-7	37	241	79	124	50	36.5	68.2
		0	37	241	81	120	85	36.4	68.4
		13	37	241	80	124	88	36.5	68.5
		14	37	241	ND	ND	ND	ND	ND
		15	37	241	80	120	80	36.4	68.4
		18	37	241	88	126	80	36.4	68.5
		21	37	241	86	123	80	36.4	68.6
		27	37	241	90	123	88	36.4	68.5
		28	37	241	86	120	85	36.5	68.5
		29	37	241	80	124	84	36.5	68.5
		35	37	241	86	122	82	36.3	68.4

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
25	1	-7	31	251	88	135	100	36.3	86.6
		0	31	251	90	138	104	36.5	86.5
		13	31	251	88	132	102	36.5	86.8
		14	31	251	86	130	100	36.5	87
		15	31	251	88	135	102	36.4	86.9
		18	31	251	85	130	100	36.6	87
		21	31	251	86	131	101	36.7	87
		27	31	251	88	130	100	36.5	87
		28	31	251	ND	ND	ND	ND	ND
		29	31	251	90	130	104	36.5	87
		35	31	251	90	130	100	36.5	87

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
26	1	-7	36	261	86	129	80	36.5	82.2
		0	36	261	80	129	84	36.4	82.2
		13	36	261	82	125	83	36.4	82.2
		14	36	261	86	123	80	36.5	82.3
		15	36	261	88	126	84	36.5	82.4
		18	36	261	84	125	83	36.4	82.3
		21	36	261	88	126	84	36.3	82.3
		27	36	261	86	125	85	36.5	82.4
		28	36	261	88	125	85	36.5	82.3
		29	36	261	88	125	86	26.6	82.4
		35	36	261	88	127	85	36.4	82.3

Equira[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
27	1	-7	41	271	88	135	110	36.5	89.8
		0	41	271	88	135	105	36.5	89.8
		13	41	271	89	136	105	36.4	90
		14	41	271	89	138	106	36.4	90
		15	41	271	90	138	105	36.5	90
		18	41	271	91	138	110	36.4	90
		21	41	271	85	135	106	36.3	90.1
		27	41	271	92	135	108	36.5	90
		28	41	271	ND	ND	ND	ND	ND
		29	41	271	86	133	105	36.4	90
		35	41	271	88	133	105	36.4	90.2

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
28	1	-7	34	281	81	122	80	36.5	64.3
		0	34	281	82	120	80	36.4	64.3
		13	34	281	80	120	81	36.4	64.2
		14	34	281	82	120	80	36.4	64.1
		15	34	281	82	122	81	36.4	64.2
		18	34	281	82	120	80	36.4	64.2
		21	34	281	82	122	82	36.3	64.2
		27	34	281	82	120	80	36.4	64.3
		28	34	281	82	122	80	36.4	64.3
		29	34	281	82	120	81	36.4	64.3
		35	34	281	82	110	80	36.4	64.2

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
29	1	-7	29	291	85	125	85	36.4	74.7
		0	29	291	84	125	85	36.4	74.7
		13	29	291	85	125	85	36.4	74.6
		14	29	291	85	125	85	36.4	74.6
		15	29	291	86	125	88	36.5	74.6
		18	29	291	84	125	85	36.4	74.7
		21	29	291	88	126	86	36.4	75
		27	29	291	85	125	84	36.5	75
		28	29	291	84	125	85	36.5	75
		29	29	291	85	125	88	36.5	75
		35	29	291	85	126	85	36.5	75

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
30	1	-7	38	301	82	130	80	36.4	71
		0	38	301	82	130	85	36.4	71.2
		13	38	301	81	125	85	36.4	71
		14	38	301	82	127	80	36.4	71.1
		15	38	301	83	126	90	36.3	71.1
		18	38	301	82	129	88	36.4	71.1
		21	38	301	82	126	85	36.4	71.1
		27	38	301	81	125	85	36.4	71.1
		28	38	301	82	130	80	36.3	71.1
		29	38	301	83	130	88	36.4	71.2
		35	38	301	82	128	96	36.4	71.2

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
1	3	-7	35	13	72	130	80	36.6	63
		0	35	13	76	140	85	36.4	63
		13	35	13	88	120	80	36	63.5
		14	35	13	74	110	70	36.2	63.5
		15	35	13	88	120	80	36	63.2
		18	35	13	80	130	80	36.4	63.3
		21	35	13	72	130	70	36.2	62.9
		27	35	13	72	135	75	36.4	63.2
		28	35	13	88	130	80	36	63
		29	35	13	78	110	70	36.2	63.2
		35	35	13	78	130	80	36.4	63.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
2	3	-7	32	23	82	140	90	36.4	68
		0	32	23	80	140	90	36.6	67.8
		13	32	23	80	130	80	36.4	69.3
		14	32	23	84	130	80	36.2	69.5
		15	32	23	92	130	90	36.2	69.3
		18	32	23	76	140	90	36.2	69.5
		21	32	23	86	130	80	36.4	68.9
		27	32	23	86	120	80	36.4	69.2
		28	32	23	88	110	70	36.2	69.8
		29	32	23	88	140	80	36.2	69.4
		35	32	23	88	130	80	36.6	69.3

Equura[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
3	3	-7	41	33	70	130	85	36.7	51.5
		0	41	33	72	120	80	36.4	51.5
		13	41	33	84	130	70	36.2	50.2
		14	41	33	88	120	70	36.0	50.2
		15	41	33	84	160	100	36	50.2
		18	41	33	84	140	80	36	50.5
		21	41	33	80	130	80	36	50
		27	41	33	80	100	60	36	51.7
		28	41	33	76	120	80	36.1	50
		29	41	33	78	130	80	36	50
		35	41	33	76	130	80	36	51

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
4	3	-7	35	43	78	110	70	36.4	49.6
		0	35	43	82	110	60	36.4	50.3
		13	35	43	76	100	60	36.2	49.8
		14	35	43	72	100	60	36.1	50.8
		15	35	43	76	110	70	36.5	51.2
		18	35	43	72	100	60	36.4	50.5
		21	35	43	76	110	70	36.2	50.5
		27	35	43	72	100	60	36.4	51.2
		28	35	43	84	110	70	36.4	50.7
		29	35	43	82	100	60	36.5	50.9
		35	35	43	82	110	60	36.5	51.2

Equoral® capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
5	3	-7	32	53	84	140	90	36.2	84.2
		0	32	53	76	130	80	36.4	84.3
		13	32	53	82	130	80	36.2	84
		14	32	53	82	130	80	36.2	84.4
		15	32	53	76	140	80	36.6	82.1
		18	32	53	82	140	85	36.4	84
		21	32	53	78	125	70	36.4	84.5
		27	32	53	80	130	80	36.2	84.3
		28	32	53	82	130	75	36.2	83.9
		29	32	53	76	130	80	36.4	84
		35	32	53	76	130	80	36.2	81.2

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
6	3	-7	36	63	76	130	70	36.2	63.5
		0	36	63	82	140	85	36.2	64
		13	36	63	76	130	75	36.4	64.2
		14	36	63	86	110	70	36.4	63.3
		15	36	63	72	130	80	36.4	63.8
		18	36	63	72	120	75	36.2	63.9
		21	36	63	82	140	90	36.2	64
		27	36	63	80	130	75	36	64
		28	36	63	76	120	70	36.2	64
		29	36	63	72	130	80	36	63.9
		35	36	63	82	120	70	36.2	63.6

Elavral capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
7	3	-7	22	73	76	130	75	36.2	83.2
		0	22	73	82	120	75	36.4	83.2
		13	22	73	72	120	70	36.2	82.8
		14	22	73	72	110	75	36.2	83.2
		15	22	73	76	120	70	36.4	83.3
		18	22	73	86	130	90	36.4	83
		21	22	73	76	140	90	36.2	82.8
		27	22	73	82	140	90	36	83.2
		28	22	73	86	130	90	36.2	83.2
		29	22	73	72	140	90	36	83.2
		35	22	73	76	130	80	36.2	82.8

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
8	3	-7	32	83	82	136	90	36.2	76.2
		0	32	83	82	140	90	36.4	76.6
		13	32	83	76	140	90	36.2	76.4
		14	32	83	84	140	90	36.2	77
		15	32	83	72	130	80	36	76.8
		18	32	83	78	140	90	36.2	77.2
		21	32	83	72	135	80	36.2	77
		27	32	83	76	130	80	36.2	77.2
		28	32	83	72	150	90	36	77
		29	32	83	76	140	90	36.2	76.8
		35	32	83	82	150	90	36	77.6

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
9	3	-7	31	93	72	130	90	36	69.8
		0	31	93	82	130	80	36.2	70
		13	31	93	76	140	90	36.2	70.5
		14	31	93	72	140	90	36.4	70.8
		15	31	93	78	150	90	36.2	71
		18	31	93	86	140	90	36.4	71.2
		21	31	93	86	130	85	36.2	71
		27	31	93	82	140	90	36	70.8
		28	31	93	76	140	90	36.2	70.8
		29	31	93	82	150	90	36.2	78.8
		35	31	93	82	150	90	36.2	71

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
10	3	-7	29	103	82	130	80	36.2	69
		0	29	103	82	120	70	36.2	68.8
		13	29	103	76	120	80	36	69.6
		14	29	103	72	130	80	36.2	69
		15	29	103	78	120	70	36.4	68.8
		18	29	103	76	120	80	36	69.2
		21	29	103	84	140	90	36.2	68.6
		27	29	103	82	140	90	36.2	69
		28	29	103	78	130	80	36.2	69
		29	29	103	78	130	90	36	69.2
		35	29	103	72	120	70	36	69.4

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
1	4	-7	26	14	70	110	80	36.67	53.45
		0	26	14	70	110	80	36.67	53
		13	26	14	88	120	80	36.67	53
		14	26	14	88	120	80	36.7	53
		15	26	14	88	120	80	36.67	53
		18	26	14	76	110	60	36.44	53
		21	26	14	70	110	80	36.67	53
		27	26	14	76	120	80	36.78	53.4
		28	26	14	76	120	82	36.72	53.5
		29	26	14	80	120	80	36.72	53.4
		35	26	14	86	110	70	36.67	53.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
2	4	-7	27	24	72	100	70	36.67	41
		0	27	24	72	100	70	36.67	41
		13	27	24	76	100	70	37.33	40.3
		14	27	24	72	106	76	36.7	41
		15	27	24	72	106	76	36.67	41.2
		18	27	24	82	110	70	37.00	40.35
		21	27	24	82	110	70	36.72	41
		27	27	24	88	100	60	36.78	41
		28	27	24	82	110	76	36.67	41
		29	27	24	90	111	78	36.67	41
		35	27	24	88	110	70	36.67	41

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
3	4	-7	30	34	66	150	100	36.67	54
		0	30	34	68	150	100	36.67	51
		13	30	34	88	140	80	37.22	55.2
		14	30	34	66	150	100	36.7	54
		15	30	34	66	150	100	36.72	54.2
		18	30	34	82	110	60	36.78	55.3
		21	30	34	67	151	100	36.72	54
		27	30	34	84	110	80	36.78	55.7
		28	30	34	80	120	80	36.67	55
		29	30	34	80	121	88	36.72	55
		35	30	34	88	130	90	36.67	55.7

Subject No.	Center No.	Day	Age	Code	Radial pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
4	4	-7	30	44	ND	110	80	36.67	48
		0	30	44	72	130	90	36.67	48
		13	30	44	82	130	80	36.67	48
		14	30	44	83	130	80	36.7	48
		15	30	44	82	125	83	36.72	48
		18	30	44	92	120	80	36.67	48
		21	30	44	92	120	80	36.67	48
		27	30	44	90	120	70	36.67	48
		28	30	44	90	125	86	36.72	48
		29	30	44	98	130	90	36.67	48.1
		35	30	44	88	130	80	36.11	48

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
5	4	-7	20	54	82	130	80	36.89	50.85
		0	20	54	82	130	80	36.89	50.8
		13	20	54	88	120	80	36.67	50
		14	20	54	87	122	80	36.7	50
		15	20	54	88	120	81	36.72	50
		18	20	54	78	120	80	36.78	51.6
		21	20	54	80	120	80	36.67	51
		27	20	54	72	110	70	36.22	50.9
		28	20	54	82	110	80	36.72	51
		29	20	54	73	115	86	36.72	51
		35	20	54					

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
6	4	-7	50	64	78	120	80	36.89	62
		0	50	64	78	125	80	36.67	63
		13	50	64	88	120	80	36.67	64
		14	50	64	88	120	80	36.7	64
		15	50	64	88	120	88	36.67	64
		18	50	64	82	120	80	36.67	64
		21	50	64	72	122	84	36.44	64
		27	50	64	76	110	80	36.78	64
		28	50	64	76	110	80	36.67	64
		29	50	64	76	110	82	36.72	64
		35	50	64	68	120	70	37.00	63

Equal® capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
7	4	-7	33	74	100	120	80	36.67	59
		0	33	74	78	120	80	36.67	59
		13	33	74	88	140	90	38.33	59.6
		14	33	74	86	140	76	36.7	59.6
		15	33	74	86	140	80	37.22	59.6
		18	33	74	82	110	80	36.67	59
		21	33	74	88	120	80	36.67	59
		27	33	74	92	120	80	36.83	59
		28	33	74	90	120	86	36.78	59
		29	33	74	90	120	80	36.72	59
		35	33	74	96	130	90	36.78	58

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
8	4	-7	33	84	72	110	70	35.78	52.35
		0	33	84	82	110	70	36.89	52.35
		13	33	84	76	120	90	36.67	53
		14	33	84	76	120	90	36.7	53
		15	33	84	78	120	70	36.67	53
		18	33	84	64	110	60	36.67	52
		21	33	84	68	100	70	37.00	53
		27	33	84	68	110	60	37.00	52
		28	33	84	68	120	66	36.67	52
		29	33	84	68	130	66	36.67	52
		35	33	84	76	110	70	36.89	52.7

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
9	4	-7	28	94	80	130	70	36.67	51
		0	28	94	80	130	80	36.89	50.7
		13	28	94	88	130	80	36.67	50.3
		14	28	94	88	130	80	36.7	50.3
		15	28	94	85	128	83	36.67	50.3
		18	28	94	88	110	70	36.33	49.2
		21	28	94	98	110	60	36.11	50.3
		27	28	94	88	120	60	37.00	50
		28	28	94	88	120	60	36.67	50
		29	28	94	88	120	68	36.67	50
		35	28	94	96	120	70	36.78	50

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
10	4	-7	40	104	86	140	90	36.89	67
		0	40	104	86	150	90	36.83	67
		13	40	104	80	140	90	36.67	67.5
		14	40	104	80	140	90	36.7	67.5
		15	40	104	80	140	90	36.67	67.5
		18	40	104	86	136	90	36.33	68
		21	40	104	68	140	90	36.78	68
		27	40	104	82	150	100	36.67	64
		28	40	104	82	150	100	36.67	64
		29	40	104	82	150	100	36.67	64
		35	40	104	68	130	90	36.44	69

Equoraf[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial pulse_rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
11	4	-7	29	114	80	140	80	36.67	69
		0	29	114	72	146	90	37.00	69
		13	29	114	84	120	90	36.67	69
		14	29	114	75	140	90	36.3	69
		15	29	114	75	135	90	36.33	69.6
		18	29	114	82	130	90	36.56	68.5
		21	29	114	92	140	90	36.33	69
		27	29	114	82	130	90	36.67	70.4
		28	29	114	82	125	90	36.56	68.5
		29	29	114	82	130	90	36.67	68.5
		35	29	114	100	130	90	37.22	70

Subject No.	Center No.	Day	Age	Code	Radial pulse_rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
12	4	-7		124	88	130	80	36.67	42.1
		0		124	82	130	80	32.78	42.5
		13		124	88	130	90	37.00	42.7
		14		124	70	130	88	36.9	42.7
		15		124	90	130	88	36.89	42.2
		18		124	80	100	60	36.67	41.5
		21		124	88	120	84	36.89	41
		27		124	84	130	80	36.67	42
		28		124	84	130	80	ND	42
		29		124	84	130	80	36.72	42
		35		124	80	130	90	36.67	42

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
13	4	-7	26	134	60	130	80	36.11	60
		0	26	134	68	130	80	36.44	61
		13	26	134	64	130	80	32.78	61
		14	26	134	65	125	88	36.4	61
		15	26	134	72	130	80	36.67	61.5
		18	26	134	72	130	80	36.67	61.5
		21	26	134	72	130	80	36.67	61
		27	26	134	82	130	80	36.44	61.5
		28	26	134	80	130	88	36.67	60.8
		29	26	134	80	128	86	36.67	61
		35	26	134	98	130	80	36.67	61.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
14	4	-7	50	144	80	130	70	36.67	58.4
		0	50	144	80	120	70	36.67	58.4
		13	50	144	98	140	70	36.78	58.4
		14	50	144	88	140	20	36.8	58.4
		15	50	144	88	140	20	36.78	58.4
		18	50	144	84	120	70	36.78	59
		21	50	144	88	120	80	36.67	59
		27	50	144	82	110	60	37.00	58.5
		28	50	144	82	110	60	37.00	58
		29	50	144	82	110	60	37.00	58
		35	50	144	ND	110	60	36.78	57

Equoral® capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
15	4	-7	28	154	84	110	70	36.67	53.5
		0	28	154	84	110	70	33.44	53.5
		13	28	154	88	130	90	36.89	53.1
		14	28	154	85	130	80	36.8	53.4
		15	28	154	80	130	88	36.72	53.4
		18	28	154	86	120	80	37.00	54.6
		21	28	154	86	120	90	37.22	53.7
		27	28	154	88	130	90	37.22	54.9
		28	28	154	88	130	90	36.78	53.4
		29	28	154	88	130	90	36.78	53.6
		35	28	154	92	120	84	36.67	53.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
16	4	-7	50	164	68	140	90	36.12	58
		0	50	164	76	134	84	36.44	58
		13	50	164	76	130	84	36.67	58
		14	50	164	78	130	84	36.3	58
		15	50	164	76	132	85	36.56	58
		18	50	164	80	120	68	36.33	58
		21	50	164	78	130	80	36.44	58.5
		27	50	164	72	140	90	36.44	58
		28	50	164	72	140	80	36.67	58
		29	50	164	80	136	82	36.67	58
		35	50	164	78	135	85	36.67	58

Enjural capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
17	4	-7	37	174	76	130	80	37.22	61
		0	37	174	82	120	80	36.94	60.5
		13	37	174	82	120	82	37.00	60.5
		14	37	174	82	122	85	37.0	60.5
		15	37	174	82	120	82	36.94	60.5
		18	37	174	80	120	70	36.67	61
		21	37	174	88	110	70	37.00	61
		27	37	174	80	110	60	36.67	61
		28	37	174	80	110	68	36.67	61
		29	37	174	80	110	68	36.67	61
		35	37	174	72	110	76	36.89	61.5

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
18	4	-7	ND	184	76	120	70	36.67	75
		0		184	76	120	80	36.94	75
		13		184	80	110	80	36.78	75
		14		184	86	110	80	36.8	75
		15		184	80	110	80	36.78	75
		18		184	80	110	70	36.67	75
		21		184	78	110	70	36.67	75
		27		184	80	110	70	36.67	75
		28		184	80	110	76	36.67	75
		29		184	80	110	76	36.72	75
		35		184	88	110	80	36.89	75

Equinal capsules

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
19	4	-7	46	194	82	130	80	36.67	55
		0	46	194	84	120	80	36.67	55
		13	46	194	88	150	80	37.06	54
		14	46	194	84	130	80	36.7	58
		15	46	194	85	130	80	36.67	58
		18	46	194	66	130	80	36.67	54
		21	46	194	72	140	80	36.67	54
		27	46	194	68	140	80	36.67	54
		28	46	194	68	140	80	36.67	54
		29	46	194	68	130	80	36.67	54
		35	46	194	72	130	80	37.00	54

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
20	4	-7	35	204	72	120	80	36.67	58
		0	35	204	82	110	70	37.22	58
		13	35	204	82	120	80	37.11	58
		14	35	204	82	110	70	37.2	58
		15	35	204	82	110	70	37.22	58
		18	35	204	84	100	60	36.78	58.2
		21	35	204	80	120	70	37.11	58.35
		27	35	204	80	100	60	36.67	54.2
		28	35	204	80	100	62	36.72	54.2
		29	35	204	80	100	60	36.67	54
		35	35	204	80	110	70	36.89	59.1

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
1	5	-7	26	15	62	120	80	36.5	67
		0	26	15	62	120	80	36.5	67
		13	26	15	62	120	80	36.5	67
		14	26	15	62	120	80	36.5	67
		15	26	15	62	120	80	36.5	67
		18	26	15	62	120	80	36.5	67
		21	26	15	62	120	80	36.5	67
		27	26	15	62	120	80	36.5	67
		28	26	15	65	120	80	36.5	67.5
		29	26	15	65	120	80	36.5	67.5
		35	26	15	74	120	80	36.5	67

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
2	5	-7	34	25	78	120	70	36.2	53.4
		0	34	25	73	120	80	36.2	54
		13	34	25	73.5	115	80	36.5	53.5
		14	34	25	71	110	75	36.4	53.3
		15	34	25	72	110	70	36.2	53.5
		18	34	25	73	110	80	36.6	54
		21	34	25	75	115	80	36.2	54.5
		27	34	25	70	110	75	36.5	54
		28	34	25	72	110	80	36.4	54
		29	34	25	73	105	80	36.5	53.5
		35	34	25	69	120	85	36.4	53.5

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
3	5	-7	37	35	73	140	80	36.6	61
		0	37	35	72	135	80	36.6	61.2
		13	37	35	73	140	80	36.9	61.1
		14	37	35	72	135	80	36.7	60.9
		15	37	35	76	130	80	36.4	61
		18	37	35	78	140	85	36.5	61.3
		21	37	35	71	130	70	36.6	61
		27	37	35	74	135	80	36.5	61.4
		28	37	35	79	130	80	36.4	61.2
		29	37	35	78	140	85	36.5	61.2
		35	37	35	78	140	80	36.5	61

Subject No.	Center No.	Day	Age	Code	Radial pulse rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Body temperature (°C)	Body weight (kg)
4	5	-7	23	45	73	120	70	36.4	70
		0	23	45	72	120	80	36.5	71
		13	23	45	73	120	75	36.2	70
		14	23	45	73	115	80	36.2	71
		15	23	45	77	115	70	36.4	70.5
		18	23	45	78	120	80	36.5	70.1
		21	23	45	80	120	85	36.7	71
		27	23	45	73	120	80	36.5	71.1
		28	23	45	81	115	70	36.5	70.8
		29	23	45	78	130	85	36.6	70.7
		35	23	45	76	110	80	36.5	71

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (b/min)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
5	5	-7	27	55	68	136	80	36.4	56
		0	27	55	73	140	80	36.5	56.1
		13	27	55	74	135	80	36.6	56
		14	27	55	71	140	80	36.4	56.2
		15	27	55	69	140	85	36.5	56.5
		16	27	55	70	145	80	36.8	56
		17	27	55	71	130	85	36.6	56.3
		18	27	55	68	140	80	36.8	56.3
		19	27	55	72	130	85	36.7	56.5
		29	27	55	70	120	80	36.8	56.4
		35	27	55	69	125	80	36.6	56.8

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (b/min)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
6	5	-7	29	65	70	130	80	36.7	73
		0	29	65	69	135	80	36.7	72.5
		13	29	65	70	125	80	36.6	72
		14	29	65	68	130	85	36.5	72.1
		15	29	65	72	130	80	36.7	72.4
		16	29	65	71	135	80	36.8	72.4
		17	29	65	73	125	80	36.5	73
		18	29	65	69	125	85	36.6	72.9
		19	29	65	70	130	80	36.5	73
		28	29	65	72	130	85	36.7	73
		29	29	65	70	130	85	36.7	72.7
		35	29	65	70	130	85	36.5	72.7

Equival capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
7	5	-7	24	75	71	148	85	36.4	69.6
		0	24	75	66	140	80	36.5	70
		13	24	75	71	140	80	36.7	70.2
		14	24	75	68	135	85	36.5	70.3
		15	24	75	71	140	85	36.4	70.1
		18	24	75	69	130	80	36.6	70
		21	24	75	72	130	80	36.7	69.8
		27	24	75	70	140	85	36.5	70.1
		28	24	75	71	140	80	36.4	70.2
		29	24	75	69	125	80	36.5	70.4
		35	24	75	68	130	80	36.7	71

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body temperature (°C)	Body weight (kg)
8	5	-7	31	85	72	130	80	36.4	75
		0	31	85	71	125	80	36.3	76
		13	31	85	71	130	80	36.5	76.1
		14	31	85	70	120	85	36.8	75.7
		15	31	85	72	130	80	36.5	75.3
		18	31	85	69	120	80	36.4	75.8
		21	31	85	68	130	80	36.6	76
		27	31	85	70	120	80	36.4	76.2
		28	31	85	69	130	80	36.5	76
		29	31	85	70	120	80	36.6	75.4
		35	31	85	71	125	85	36.5	76.2

Equival[®] capsules

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
9	5	-7	28	95	75	120	80	36.6	71.8
		0	28	95	73	120	75	36.7	73
		13	28	95	72	120	80	36.6	72
		14	28	95	75	110	80	36.7	72.5
		15	28	95	70	120	75	36.5	72
		18	28	95	71	115	75	36.8	71.5
		21	28	95	72	120	80	36.7	72
		27	28	95	69	120	80	36.5	71
		28	28	95	71	120	80	36.6	71
		29	28	95	70	110	70	36.5	71.8
		35	28	95	69	120	80	36.7	72.6

Subject No.	Center No.	Day	Age	Code	Radial_pulse_rate (bpm)	Systolic_pressure (mmHg)	Diastolic_pressure (mmHg)	Body_temperature (°C)	Body_weight (kg)
10	5	-7	33	105	69	110	80	36.5	69
		0	33	105	68	110	85	36.5	68
		13	33	105	70	110	80	36.7	70
		14	33	105	67	120	80	36.5	68.5
		15	33	105	71	100	80	36.7	70.1
		18	33	105	69	110	80	36.8	69
		21	33	105	68	100	75	36.4	69.6
		27	33	105	67	120	80	36.6	70.4
		28	33	105	66	110	80	36.5	70.1
		29	33	105	69	110	85	36.5	70.9
		35	33	105	67	120	80	36.6	70.5

Value -- clinically relevant value

16. Appendices**16.3 Case Report Forms****16.3.1 CRFs for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events**

Equoral® capsules

**16.3.1 GRFs for Deaths, Other Serious Adverse Events and Withdrawals
for Adverse Events**

Not applicable

16. Appendices

16.3 Case Report Forms

16.3.2 Other CRFs Submitted

16.3.2 Other CRFs Submitted

Not applicable

16. Appendices

16.4 Individual Patient Data Listings (US Archival Listings)

Equoral® capsules

18.4 Individual Patient Data Listings (US Archival Listings)

Not applicable