8. Bioequivalence Studies

Bioequivalence study was performed between Amoxil 500 mg capsules (Reference Formulation) manufactured by GlaxoSmithKline, UK and Amoxicillin 500 mg capsules (Test Formulation) of Aurobindo Pharma Limited, India. are bioequivalent when conducted on 24 healthy, adult, male human subjects under fasting conditions.

The details of the batches used in this study are as follows:

Test (T) : Amoxicillin Capsules 500mg

Mfg. By : Aurobindo Pharma Limited, India.

Batch No : ANBCB4001

Mfg. Date : 06/2004

Expiry date : 05/2006

Reference(R) : Amoxil Capsules 500 mg

Mfg. By : GlaxoSmithKline, UK

Batch No. : 85484 A

Expiry Date : 12/2006

The detailed Bioequivalence summary report is presented herewith.

APL RESEARCH CENTRE
(A Division of Aurobindo Pharma Ltd.)

QUALITY ASSURANCE DEPARTMENT
APL RESEARCH CENTRE
313, BACHUPALLY, QUTHUBULLAPUR MANDAL, HYDERABAD, 500 072
INDIA.

SOP NO. APL-QAD-004-00
FORM No. 01

QUALITY ASSURANCE AUTHENTICATION

Study No.: Amx-06/04

Project Title: An open label randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, comparative oral bioavailability study of Amoxicillin 500mg capsules (Test) of Aurobindo Pharma Ltd., India and Amoxil (Reference) capsules of GlaxoSmithkline, UK in 24 healthy, adult, male, human subjects under fasting conditions.

The conduct of this study has been subjected to periodic inspections as mentioned below and the Quality Assurance Unit has audited this report.

Date of Inspection/Audit	Phase
18th Oct 2004	Protocol and ICF preparation
10th & 11th, 19th & 20th Nov 2004	Clinical phase
14th – 17th Feb 2005	Bioanalytical phase
26th Nov 04, 14th –16th Feb 2005	Data audit
15th – 16th, 17th Feb 2005	Report Phase

This report accurately describes that the methods and procedures used in the study and the reported results accurately reflect the raw data of the study.

S. Ravi Sankar

Dr. S. Ravi Sankar, M.Pharm, Ph.D, MBA, FIC.,
Head - Quality Assurance Department

Date: 23rd February 2005

APL RESEARCH CENTRE
CLINICAL PHARMACOLOGY DEPARTMENT

Study No:Amx-06/04

An Open Label, Randomized, Two Treatment, Two Sequence, Two Period, Cross-Over, Single-Dose Comparative Oral Bioavailability Study Of Amoxicillin 500 mg Capsules (Test) Of Aurobindo Pharma Ltd., India And Amoxil (Reference) Capsules Of GlaxoSmithKline, UK In 24 Healthy, Adult, Male, Human Subjects Under Fasting Conditions.

SUMMARY REPORT

Date: 14th February, 2005

[Volume 1]

APL RESEARCH CENTRE
Survey No. 313, Bachupally Village, Quthubullapur Mandal,
HYDERABAD, 500072
INDIA
PHONE No.: 040-23040261/263

TABLE OF CONTENTS

1.0 COMPLIANCE STATEMENT:

We attest to the fact that the data presented here is accurate and reflects the raw data. The study has been conducted as per the Protocol and SOPs of CPD, APL Research Centre and we accept the responsibility for scientific correctness of the project and the validity of the data produced in this report.

Principal Investigator &

Investigator- Pharmacokinetics:

Mr. N.Nagaraj Kumar (M. Pharm)
CPD, PK & BS Unit,
APL Research Centre,
313, Bachupally, Quthubullapur Mandal,
Hyderabad-500 072
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14/02/05

Signature

Investigator-Biostatistics:

Mr. P. Pramod Kumar Reddy (M. Sc)
CPD, PK & BS Unit,
APL Research Centre,
313, Bachupally, Quthubullapur Mandal,
Hyderabad-500 072
India.

14/02/05

Signature

2.0 SYNOPSIS

Study Title	An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules (Test) of Aurobindo Pharma Ltd., India and Amoxil (Reference) capsules of GlaxoSmithKline, UK in 24 healthy, adult, male, human subjects under fasting conditions.
Objective	To compare the rate and extent of absorption of Amoxicillin capsules (Test) of Aurobindo Pharma Ltd., India with that of Amoxil capsules (Reference) of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), when given in equal doses of single oral dose containing 500 mg of Amoxicillin in 24 healthy, adult, male, human subjects under fasting conditions.
Products Evaluated **Test:** **Reference:**	Test (T) : Amoxicillin capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin. Mfg. By : Aurobindo Pharma Ltd., India Batch No : ANBCB 4001 Mfg. Date: 06/2004 Expiry Date: 05/2006 Reference(R): Amoxil capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin. Mfg. By : GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK). Batch No : 85484 A Expiry Date : 12/2006
Investigators:	Dr. Nitin Kulkarni, Mr N. Nagaraj Kumar, Mr. Avinash. B. Gaikwad, Mr.P. Pramod Kumar Reddy.
Dosing Dates: **Period I:** **Period II:**	 On 11th November, 2004 between 8:00 and 8:12 AM On 20th November , 2004 between 8:00 and 8:12 AM
Methodology	Serial blood samples were drawn before dosing and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 12.0 hours post-dose. Analysis of plasma concentrations for Amoxicillin was by a validated LC-MS-MS method using precipitation technique. Calculation of pharmacokinetic parameters was done using drug concentration time profiles by non-compartmental methods. Statistical comparison of the pharmacokinetic parameters of the two formulations was made to assess bioequivalence.
Number of Subjects (Admission & Stay)	24 + 4 (standby) healthy male subjects enrolled as per protocol. There was a washout period of 9 days between the two periods of the study.
Main Inclusion Criteria	Healthy adult male subjects aged 18-50 years.

Dose Administration	After a supervised overnight fast of 10 hours, subjects received a single oral dose of the assigned formulation, with 240 mL water, according to the randomization scheme.
Blood Sampling Procedure	Blood samples collected at times specified under study design, and centrifuged under refrigeration as soon as possible after collection. All plasma samples stored in suitably labeled tubes below –20° C and finally below –70°C until analysis. Samples were drawn via an indwelling catheter and using heparin-lock technique. Before each blood draw 1.0 mL of the blood was discarded so as to prevent the heparin from interfering with the analysis.
Analyte Measured	Amoxicillin was measured by using validated LC-MS-MS method (LOQ = 0.189 µg/mL as in study sample analysis; calibration curve range from 0.189 µg/mL to 15.578 µg/mL) at Bioanalytical Unit of APL-CPD. Ampicillin Trihydrate was used as the internal standard.
Analytical Phase Dates	Initiation date: 23rd January, 2005 Completion Date: 28th January, 2005
Evaluation Criteria	The 90% Confidence Intervals were constructed for the ratios of the means of Lntransformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} of Amoxicillin for the test and reference formulations. Bioequivalence is to be concluded if the confidence intervals fall within the bioequivalence limits of 80%-125%.
Statistical Methods	PROC GLM of SAS® software release 8.2 was employed for statistical analysis.
Protocol and/or SOP Deviation	The protocol and / or SOP deviation during the clinical, analytical and statistical phase of the study are mentioned in the respective reports.
Result	The 90% confidence intervals for Amoxicillin 500 mg Capsules (Test) manufactured by Aurobindo Pharma Ltd., India and Amoxil Capsules of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), for Lntransformed parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} were 94.51-111.69%, 96.76-106.89% and 97.06-106.95% respectively.
Conclusion	The statistical report clearly indicates that the pharmacokinetic parameters for Amoxicillin 500 mg Capsules (Test) manufactured by Aurobindo Pharma Ltd., India and Reference formulations manufactured by GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), are within the 80-125% acceptance range and therefore the test product is bioequivalent to the reference product of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), under fasting conditions in the present study population.

3.0 FACILITIES

3.1 Clinical Facility and Clinical Investigations Unit

Clinical Pharmacology Department,
APL Research Centre,
Plot No. 33-35,2nd and 3rd floor,
Alluri Sitaramaraju Nagar,
Opp J.P.N. Nagar,
Mirra Multi-speciality Hospital,
Miyapur
Hyderabad-500 050
INDIA.

3.2 Bioanalytical, Pharmacokinetic and Statistical Operations

Clinical Pharmacology Department
APL Research Centre,
313, Bachupally,
Quthubullapur Mandal,
Hyderabad – 500 072.
INDIA.

4.0 OBJECTIVE

An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules (Test) of Aurobindo Pharma Ltd., India and Amoxil (Reference) capsules of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), in 24 healthy, adult, male, human subjects under fasting conditions.

5.0 PRODUCTS EVALUATED

Test (T) : Amoxicillin Capsules containing Amoxicillin as Trihydrate equivalent to 500 mg of Amoxicillin.

Mfg. By : Aurobindo Pharma Ltd., India

Batch No : ANBCB 4001

Mfg. Date: 06/2004 Expiry Date: 05/2006

Reference(R): Amoxil Capsules containing Amoxicillin as Trihydrate equivalent to 500 mg of Amoxicillin.

Mfg. By : GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK).

Batch No : 85484 A

Expiry Date : 12/2006

6.0 STUDY DESIGN

Open label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules in 24 healthy, adult, male, human subjects under fasting conditions

7.0 NUMBER OF SUBJECTS

24 + 4 healthy male subjects were enrolled as per protocol. The subjects checked into the clinical facility on 10th November 2004 for period 19th November 2004 and I for period II.

There was a washout period of 9 days between the two periods.
For more details refer to the clinical report (Volume 2)

8.0 DOSE ADMINISTRATION

After a supervised overnight fast, subjects received a single oral dose of the assigned formulation, with 240 mL water, according to the randomization scheme. The dosing dates were as follows:
Period I : On 11th November 2004 between 8.00 and 8.12 AM
Period II: On 20th November 2004 between 8.00 and 8.12 AM

9.0 BLOOD SAMPLE COLLECTION AND STORAGE

Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 12.0 hours post-dose as described under the protocol (Study No; Amx-06/04), and plasma separated by centrifugation under refrigerated condition. The plasma was transferred to labeled tubes and stored below – 20° C and finally below –70°C at the clinical unit. The samples were transferred to the bioanalytical unit under frozen condition and stored in the deep freezer below –70° C until analysis.

10.0 SUBJECT WITHDRAWALS AND DROPOUTS

There were no withdrawals and dropouts in the study.

11.0 ANALYTE MEASURED

Amoxicillin was measured in plasma by a validated LC-MS-MS method using precipitation technique as described in the method SOP no: CPD- BA- M-11-01.
For Amoxicillin the LOQ = 0.189 µg /mL was used in study sample analysis, at the bioanalytical unit of Aurobindo Pharma Limited, Research Centre. The calibration curve ranged from 0.189 µg /mL to 15.578 µg /mL.
Ampicillin Trihydrate was used as the Internal Standard (IS).

11.1 Dates of Analytical Phase

The dates for the Analytical phase were:
Initiation Date: 23rd January 2005
Completion Date: 28th January 2005
(Refer to Bioanalytical Report Volume 3 for more details).

12.0 PHARMACOKINETIC ANALYSIS

The Pharmacokinetic parameters for plasma Amoxicillin concentrations were calculated using the NCA (Non compartmental analysis) model of WinNonlin Version 3.3. A total of 24 subjects were analysed for the determination of pharmacokinetic parameters.

13.0 STATISTICAL ANALYSIS

PROC GLM of SAS® software release 8.2 was employed for statistical analysis. Refer to the statistical report Vol. 4, for more details.

14.0 PROTOCOL AND/OR SOP DEVIATIONS

The protocol and / or SOP deviation during the clinical, bioanalytical and statistical phase of this study are mentioned in the respective reports.

15.0 RESULTS AND DISCUSSIONS

The individual and mean plasma concentrations of Amoxicillin for Test and Reference products are listed in Table 1 and 2 respectively. The comparative pharmacokinetic parameters of Amoxicillin for each treatment are listed in Table 3. The summary statistics of Pharmacokinetic parameters of Amoxicillin are presented in Table 4.

The mean and semi-log plots of plasma Amoxicillin concentrations are plotted in Figure 1 and 2.

Individual subject semi-log profiles of Amoxicillin are plotted in figures 3 to 26.

The median T_{max} values for Amoxicillin in Amoxicillin 500 mg Capsules (Test) manufactured by Aurobindo Pharma Ltd., India and Amoxil Capsules (Reference) of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), was 2.00 and 2.17 hours, respectively.

The 90% confidence intervals, for Amoxicillin Capsules (Test) manufactured by Aurobindo Pharma Ltd., India, and Amoxil Capsules (Reference) of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), Ln-transformed parameters for C_{max}, AUC_{0-t}, and AUC_{0-inf} were 94.51-111.69%, 96.76-106.89% and 97.06-106.95% respectively

16.0 CONCLUSION

The statistical report clearly indicates that the pharmacokinetic parameters of Amoxicillin 500 mg Capsules (Test) manufactured by Aurobindo Pharma Ltd., India and Amoxil Capsules of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), are within the 80-125% acceptance range.

Based on these results, the Amoxicillin 500 mg Capsules (Test) manufactured by Aurobindo Pharma Ltd., India, are bioequivalent to the reference product of GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK), under fasting conditions in the present study population.

17.0 LIST OF TABLES

TABLE 1

Individual and Mean Plasma Amoxicillin Concentration (µg/mL) for Test

Treatment	Subject	Sequence	Concentration (µg/mL)															
			Time (hr)															
			0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.33	2.67	3.00	4.00	5.00	6.00	7.00	8.00	12.00
T	1	RT	0.000	0.000	0.568	1.193	2.826	4.412	5.191	5.194	4.574	4.606	3.387	1.516	1.012	0.519	0.372	0.219	0.000
	2	TR	0.000	0.000	0.000	0.968	1.673	3.517	4.453	5.662	5.610	5.027	3.979	2.343	1.198	0.554	0.348	0.000	0.000
	3	RT	0.000	0.000	1.500	4.518	5.974	7.085	7.216	7.643	5.863	4.832	4.824	2.599	1.505	0.925	0.546	0.431	0.000
	4	TR	0.000	0.000	0.335	1.229	2.136	2.341	2.893	3.955	5.123	5.942	4.139	2.296	1.390	0.662	0.379	0.222	0.000
	5	TR	0.000	0.000	2.251	4.120	5.444	8.084	7.775	6.556	5.881	4.602	2.918	1.356	0.879	0.459	0.339	0.202	0.000
	6	RT	0.000	0.000	0.527	1.968	2.465	5.353	4.854	5.571	5.610	5.899	5.526	3.668	2.481	1.455	0.541	0.351	0.000
	7	RT	0.000	0.000	0.228	1.773	2.744	2.578	3.242	4.606	5.644	8.318	8.958	6.270	2.613	1.680	0.970	0.615	0.000
	8	TR	0.000	0.000	0.708	3.529	5.995	6.497	6.279	5.461	4.776	3.822	3.633	2.023	1.193	0.734	0.457	0.297	0.000
	9	TR	0.000	0.000	0.958	3.517	5.828	6.525	8.245	8.137	6.614	4.846	3.458	2.072	1.328	0.740	0.388	0.245	0.000
	10	RT	0.000	0.000	0.449	1.480	2.399	2.788	2.756	3.574	4.710	5.995	5.885	3.988	2.455	1.509	0.765	0.419	0.000
	11	RT	0.000	0.000	2.314	4.399	6.640	7.132	6.600	5.562	4.558	3.882	2.750	1.328	0.699	0.425	0.233	0.000	0.000
	12	TR	0.000	0.000	0.414	1.198	1.555	2.262	5.785	6.408	5.529	4.265	2.837	1.336	0.679	0.372	0.233	0.000	0.000
	13	RT	0.000	0.484	2.053	3.648	1.684	4.605	5.269	5.061	4.855	4.879	4.277	2.880	2.005	1.544	0.996	0.572	0.000
	14	TR	0.000	0.498	3.266	5.125	6.315	7.706	7.638	6.846	4.901	3.845	2.661	1.174	0.731	0.444	0.264	0.132	0.000
	15	RT	0.000	0.259	2.969	5.336	8.396	9.741	10.075	9.281	7.941	6.047	4.941	2.303	1.431	0.796	0.517	0.295	0.000
	16	TR	0.000	0.000	1.688	5.605	7.714	7.961	7.706	6.453	5.997	4.745	3.535	2.010	1.056	0.673	0.360	0.229	0.000
	17	RT	0.000	0.000	0.382	2.891	4.879	6.185	5.353	5.254	5.689	5.171	4.466	3.044	1.690	1.192	0.470	0.328	0.000
	18	TR	0.000	0.000	0.881	1.908	2.362	3.527	4.692	5.999	5.144	4.914	4.184	2.223	1.158	0.654	0.367	0.201	0.000
	19	RT	0.000	0.000	0.968	2.462	3.414	4.578	5.369	5.450	4.560	4.959	3.248	2.459	1.799	0.938	0.542	0.337	0.000
	20	TR	0.000	0.000	0.000	0.468	0.960	2.601	4.709	8.840	9.068	7.527	5.865	2.608	1.289	0.824	0.464	0.277	0.000
	21	TR	0.000	0.000	1.061	3.025	4.705	5.056	4.215	3.773	3.438	3.398	3.027	1.833	0.971	0.636	0.337	0.000	0.000
	22	RT	0.000	0.000	0.381	0.749	2.049	2.893	5.604	7.411	7.640	6.663	5.388	2.898	1.594	0.970	0.533	0.302	0.000
	23	RT	0.000	0.000	0.983	3.873	6.538	9.398	9.835	8.756	8.444	6.788	6.142	3.373	1.828	1.082	0.641	0.346	0.000
	24	TR	0.000	0.000	0.727	1.527	2.858	4.733	8.416	8.696	7.794	6.732	5.592	2.644	1.326	0.681	0.369	0.000	0.000
		N	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
		Mean	0.000	0.052	1.067	2.771	4.065	5.315	6.007	6.256	5.832	5.321	4.401	2.510	1.430	0.853	0.476	0.251	0.000
		SD	0.0000	0.1452	0.9105	1.5680	2.2052	2.2906	2.0120	1.6539	1.4061	1.2376	1.4664	1.0882	0.5486	0.3789	0.2007	0.1710	0.0000
		Min	0.000	0.000	0.000	0.468	0.960	2.262	2.756	3.574	3.438	3.398	2.661	1.174	0.679	0.372	0.233	0.000	0.000
		Median	0.000	0.000	0.804	2.677	3.136	4.895	5.487	5.831	5.610	4.937	4.162	2.323	1.327	0.737	0.423	0.261	0.000
		Max	0.000	0.498	3.266	5.605	8.396	9.741	10.075	9.281	9.068	8.318	8.958	6.270	2.613	1.680	0.996	0.615	0.000
		CV%	Missing	280.88	85.33	56.58	54.25	43.10	33.49	26.44	24.11	23.26	33.32	43.35	38.38	44.43	42.14	68.16	Missing

Missing = Cannot be Calculated

LOQ = 0.189 µg/mL

TABLE 2

Individual and Mean Plasma Amoxicillin Concentration (µg/mL) for Reference

			Concentration (µg/mL)																
			Time (hr)																
Treatmen	Subject	Sequence	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.33	2.67	3.00	4.00	5.00	6.00	7.00	8.00	12.00
R	1	RT	0.000	0.337	2.046	3.880	5.175	5.567	4.596	3.299	2.258	1.240	0.922	0.400	0.240	0.000	0.000	0.000	0.000
	2	TR	0.000	0.000	0.431	1.365	2.665	3.985	5.440	5.422	5.768	6.158	5.463	3.676	2.349	1.100	0.576	0.287	0.000
	3	RT	0.000	0.000	0.716	2.228	3.125	5.009	6.191	7.197	5.917	5.138	3.766	1.990	1.131	0.689	0.454	0.263	0.000
	4	TR	0.000	0.000	0.644	2.556	4.045	5.508	6.853	7.626	7.606	7.178	6.588	3.698	1.962	0.898	0.466	0.389	0.000
	5	TR	0.000	0.000	1.142	2.812	4.123	7.221	9.654	10.026	8.641	7.367	6.367	3.057	1.949	0.986	0.835	0.375	0.000
	6	RT	0.000	0.000	0.288	1.106	1.617	2.118	2.614	3.117	3.213	3.473	3.381	2.656	1.592	0.884	0.493	0.310	0.000
	7	RT	0.000	0.000	0.761	1.163	1.762	2.616	3.963	6.720	7.447	6.492	4.430	2.124	1.096	0.553	0.365	0.201	0.000
	8	TR	0.000	0.000	1.715	4.887	9.797	10.154	13.799	11.488	10.441	8.625	6.955	3.545	1.872	1.262	0.754	0.488	0.000
	9	TR	0.000	0.000	1.337	5.414	9.107	10.987	10.620	10.004	8.710	6.893	5.414	2.911	1.577	0.884	0.571	0.294	0.000
	10	RT	0.000	0.000	0.345	0.911	1.317	1.580	2.065	2.706	3.169	2.867	2.958	2.491	1.416	0.731	0.455	0.243	0.000
	11	RT	0.000	0.000	0.797	1.141	1.552	2.819	3.953	4.864	4.868	3.624	2.836	1.135	0.504	0.277	0.205	0.000	0.000
	12	TR	0.000	0.000	0.312	1.018	3.541	5.017	6.528	6.539	6.088	4.693	3.683	1.765	0.907	0.541	0.273	0.000	0.000
	13	RT	0.000	0.000	0.954	2.635	3.816	5.330	5.475	5.091	4.793	4.417	4.280	2.587	1.592	1.036	0.762	0.424	0.000
	14	TR	0.000	0.000	1.239	3.287	4.204	6.843	7.716	8.434	6.594	4.864	3.587	1.615	0.873	0.521	0.351	0.249	0.000
	15	RT	0.000	0.000	0.774	3.094	5.776	7.265	7.721	6.547	5.168	4.296	3.319	1.844	1.111	0.626	0.427	0.210	0.000
	16	TR	0.000	0.000	1.727	3.056	5.228	7.956	8.859	8.954	9.587	7.956	7.108	3.760	2.183	1.164	0.694	0.381	0.000
	17	RT	0.000	0.000	0.000	0.261	0.686	1.262	2.541	3.988	5.262	5.410	4.115	2.739	1.478	0.701	0.451	0.239	0.000
	18	TR	0.000	0.000	0.759	1.916	2.455	2.428	4.799	5.419	5.046	5.705	5.484	3.658	2.054	1.123	0.544	0.328	0.000
	19	RT	0.000	0.000	0.417	1.244	1.551	1.903	2.629	4.683	3.827	3.243	2.237	2.677	0.681	1.315	0.481	0.295	0.000
	20	TR	0.000	0.000	1.229	2.175	3.638	6.057	9.525	11.484	8.561	7.886	6.336	3.373	2.432	1.105	0.818	0.402	0.000
	21	TR	0.000	0.000	0.423	1.177	2.321	3.187	5.804	5.366	8.902	8.524	7.585	3.546	2.014	1.028	0.606	0.302	0.000
	22	RT	0.000	0.000	0.000	0.210	0.311	0.487	0.471	1.038	2.384	2.796	2.859	4.732	3.672	1.762	0.710	0.404	0.000
	23	RT	0.000	0.000	0.255	1.172	2.515	3.997	4.116	5.183	5.577	4.191	5.065	2.643	1.645	0.769	0.384	0.249	0.000
	24	TR	0.000	0.000	0.876	1.970	2.406	3.175	4.660	5.353	6.128	6.665	8.685	7.299	3.086	1.391	0.756	0.324	0.000
		N	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
		Mean	0.000	0.014	0.799	2.112	3.447	4.686	5.858	6.273	6.081	5.404	4.726	2.913	1.642	0.889	0.518	0.277	0.000
		SD	0.0000	0.0688	0.5439	1.3450	2.3387	2.7481	3.1009	2.7316	2.2793	2.0013	1.9060	1.3458	0.7919	0.3802	0.2049	0.1290	0.0000
		Min	0.000	0.000	0.000	0.210	0.311	0.487	0.471	1.038	2.258	1.240	0.922	0.400	0.240	0.000	0.000	0.000	0.000
		Median	0.000	0.000	0.760	1.943	2.895	4.503	5.458	5.421	5.843	5.274	4.355	2.708	1.592	0.891	0.487	0.295	0.000
		Max	0.000	0.337	2.046	5.414	9.797	10.987	13.799	11.488	10.441	8.625	8.685	7.299	3.672	1.762	0.835	0.488	0.000
		CV%	Missing	489.90	68.04	63.70	67.84	58.64	52.93	43.55	37.48	37.03	40.33	46.19	48.22	42.75	39.56	46.52	Missing

Missing = Cannot be Calculated

LOQ = 0.189 µg/mL

TABLE 3

Comparative Evaluation of Pharmacokinetic Parameters of Amoxicillin

Subject	Sequence	Tmax (hr)		Cmax (µg/mL)		No of points for kel		AUC last (hr*µg/mL)		kel (1/hr)		kel start (hr)		kel stop (hr)		T1/2 (hr)		AUC INF (hr*µg/mL)		AUC % Extrap (%)	
		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment	
		R	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T
1	RT	1.33	2.00	5.567	5.194	4	5	9.865	15.047	0.71	0.49	2.67	4.00	5.00	8.00	0.97	1.42	10.202	15.497	3.31	2.90
2	TR	2.67	2.00	6.158	5.662	3	6	21.641	15.744	0.67	0.63	6.00	2.67	8.00	7.00	1.03	1.10	22.068	16.296	1.94	3.39
3	RT	2.00	2.00	7.197	7.643	5	9	18.373	23.131	0.50	0.49	4.00	2.00	8.00	8.00	1.40	1.41	18.903	24.005	2.80	3.64
4	TR	2.00	2.67	7.626	5.942	8	3	25.183	15.366	0.58	0.55	2.33	6.00	8.00	8.00	1.19	1.27	25.852	15.773	2.59	2.58
5	TR	2.00	1.33	10.026	8.084	9	5	27.757	19.234	0.54	0.48	2.00	4.00	8.00	8.00	1.28	1.46	28.448	19.658	2.43	2.16
6	RT	2.67	2.67	3.473	5.899	5	6	13.699	22.447	0.55	0.57	4.00	3.00	8.00	8.00	1.27	1.21	14.266	23.060	3.97	2.66
7	RT	2.33	3.00	7.447	8.958	6	4	17.268	27.241	0.61	0.49	3.00	5.00	8.00	8.00	1.13	1.42	17.596	28.498	1.87	4.41
8	TR	1.67	1.33	13.799	6.497	4	4	34.996	18.732	0.45	0.46	5.00	5.00	8.00	8.00	1.52	1.49	36.069	19.371	2.97	3.30
9	TR	1.33	1.67	10.987	8.245	9	6	29.786	21.231	0.59	0.54	2.00	3.00	8.00	8.00	1.18	1.29	30.285	21.686	1.65	2.10
10	RT	2.33	2.67	3.169	5.995	5	3	12.014	20.641	0.58	0.64	4.00	6.00	8.00	8.00	1.20	1.08	12.433	21.295	3.38	3.07
11	RT	2.33	1.33	4.868	7.132	7	4	11.558	17.264	0.71	0.57	2.33	4.00	7.00	7.00	0.97	1.21	11.845	17.672	2.43	2.31
12	TR	2.00	2.00	6.539	6.408	8	4	16.795	13.335	0.65	0.58	2.00	4.00	7.00	7.00	1.06	1.19	17.214	13.734	2.43	2.90
13	RT	1.67	1.67	5.475	5.269	7	3	19.424	20.829	0.44	0.50	2.67	6.00	8.00	8.00	1.58	1.40	20.388	21.981	4.73	5.24
14	TR	2.00	1.33	8.434	7.706	3	5	19.719	18.831	0.37	0.54	6.00	4.00	8.00	8.00	1.88	1.29	20.394	19.076	3.31	1.28
	RT	1.67	1.67	7.721	10.075	10	5	19.313	27.443	0.56	0.51	1.67	4.00	8.00	8.00	1.24	1.35	19.688	28.018	1.90	2.05
	TR	2.33	1.33	9.587	7.961	8	10	29.895	21.601	0.57	0.57	2.33	1.67	8.00	8.00	1.21	1.21	30.560	22.001	2.18	1.82
	RT	2.67	1.33	5.410	6.185	7	8	14.654	21.000	0.58	0.52	2.67	2.33	8.00	8.00	1.19	1.34	15.065	21.635	2.72	2.93
	TR	2.67	2.00	5.705	5.999	5	4	20.381	16.770	0.62	0.58	4.00	5.00	8.00	8.00	1.13	1.19	20.915	17.114	2.55	2.01
	RT	2.00	2.00	4.683	5.450	3	3	13.086	18.234	0.75	0.51	6.00	6.00	8.00	8.00	0.93	1.35	13.481	18.892	2.93	3.49
	TR	2.00	2.33	11.484	9.068	9	3	28.568	20.545	0.54	0.55	2.00	6.00	8.00	8.00	1.28	1.27	29.309	21.053	2.53	2.41
	TR	2.33	1.33	8.902	5.056	7	6	24.083	14.648	0.63	0.53	2.67	2.67	8.00	7.00	1.10	1.30	24.563	15.278	1.96	4.12
	RT	4.00	2.33	4.732	7.640	4	3	15.521	20.689	0.75	0.58	5.00	6.00	8.00	8.00	0.92	1.19	16.057	21.207	3.34	2.44
23	RT	2.33	1.67	5.577	9.835	6	8	17.720	28.727	0.62	0.56	3.00	2.33	8.00	8.00	1.12	1.23	18.124	29.343	2.23	2.10
24	TR	3.00	2.00	8.685	8.696	5	4	28.556	22.087	0.76	0.66	4.00	4.00	8.00	7.00	0.91	1.05	28.980	22.649	1.46	2.48
	N	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	Mean	2.22	1.90	7.219	7.108	6.13	5.04	20.411	20.034	0.60	0.55	3.39	4.11	7.79	7.79	1.20	1.28	20.946	20.616	2.65	2.83
	SD	0.571	0.507	2.6400	1.5184	2.112	2.010	6.8144	4.0262	0.100	0.052	1.382	1.433	0.658	0.415	0.226	0.119	6.9363	4.1418	0.761	0.902
	Min	1.33	1.33	3.169	5.056	3.00	3.00	9.865	13.335	0.37	0.46	1.67	1.67	5.00	7.00	0.91	1.05	10.202	13.734	1.46	1.28
	Median	2.17	2.00	6.868	6.815	6.00	4.50	19.369	20.593	0.59	0.54	2.84	4.00	8.00	8.00	1.18	1.28	20.038	21.130	2.54	2.62
	Max	4.00	3.00	13.799	10.075	10.00	10.00	34.996	28.727	0.76	0.66	6.00	6.00	8.00	8.00	1.88	1.49	36.069	29.343	4.73	5.24
	CV%	25.68	26.65	36.57	21.36	34.49	39.88	33.39	20.10	16.74	9.49	40.77	34.86	8.44	5.32	18.92	9.27	33.12	20.09	28.70	31.93

TABLE 4

Summary Statistics of Pharmacokinetic Parameters of Amoxicillin

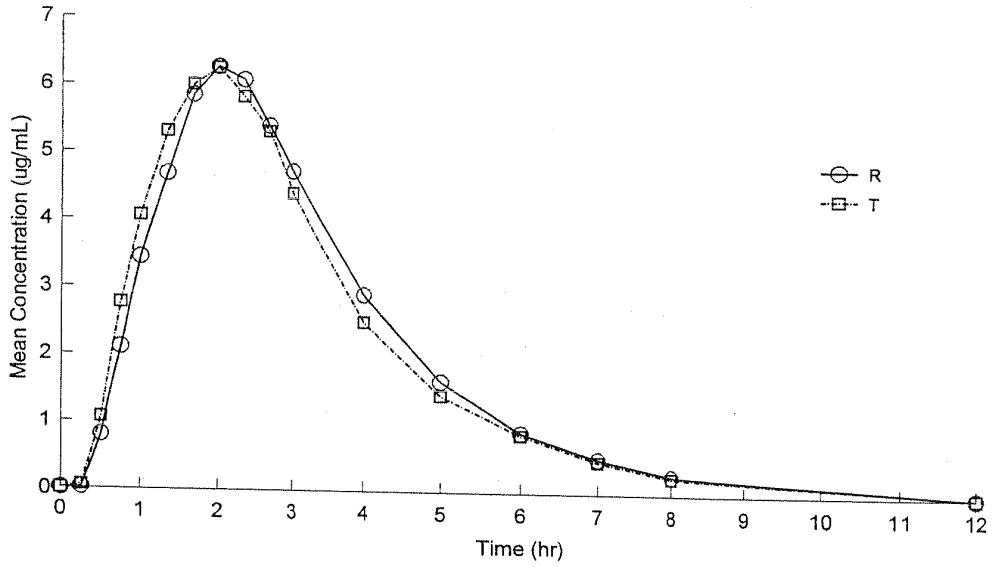
Statistics			C_{max} (µg/mL)	AUC_{0-t} (hr.µg/mL)	AUC_{0-inf} (hr.µg/mL)	T_{max} (hr)*
Test Formulation	N		24	24	24	24
	Mean		7.108	20.034	20.616	2.00
	S.D.		1.5184	4.0262	4.1418	0.507
	C.V.(%)		21.36	20.10	20.09	26.65
Reference Formulation	N		24	24	24	24
	Mean		7.219	20.411	20.946	2.17
	S.D.		2.6400	6.8144	6.9363	0.571
	C.V.(%)		36.57	33.39	33.12	25.68
ANOVA p-value	Untransformed	Sequence	0.0092	0.0350	0.0412	-
		Period	<0.0001	<0.0001	<0.0001	-
		Treatment	0.7657	0.5874	0.6405	-
	Lntransformed	Sequence	0.0074	0.0359	0.0415	-
		Period	<0.0001	<0.0001	<0.0001	-
		Treatment	0.5841	0.5666	0.5153	-
Least Square Mean	Test		7.108	20.034	20.616	-
	Reference		7.219	20.411	20.946	-
Geometric Mean	Test		6.96	19.65	20.23	-
	Reference		6.77	19.33	19.85	-
Ratio (T/R %)	Lntransformed		102.74	101.70	101.89	-
Intra-subject CV (%)			16.97	10.07	9.81	-
90 % Confidence Interval	Lntransformed	Lower	94.51	96.76	97.06	-
		Upper	111.69	106.89	106.95	-
		Power (%)	100	100	100	-

For T_{max} instead of mean, median has been used.

18.0 LIST OF FIGURES

FIGURE 1

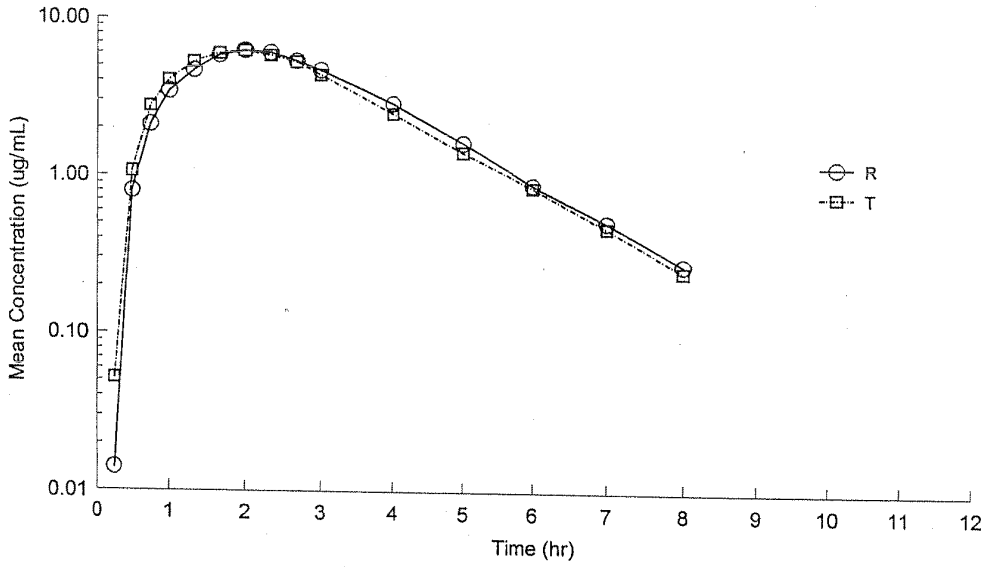
Linear Plot Of Mean Plasma Amoxicillin Concentrations Versus Time In Adult, Healthy, Male Human Subjects (N=24)



User Chart
C:\CPD-BE\Amoxicillin\Amx0604\linear mean plot.pco (14-Feb-2005)

FIGURE 2

Semi – log Plot of Mean Plasma Amoxicillin Concentrations Versus Time in Adult, Healthy, Male, Human Subjects (N=24)



User Chart
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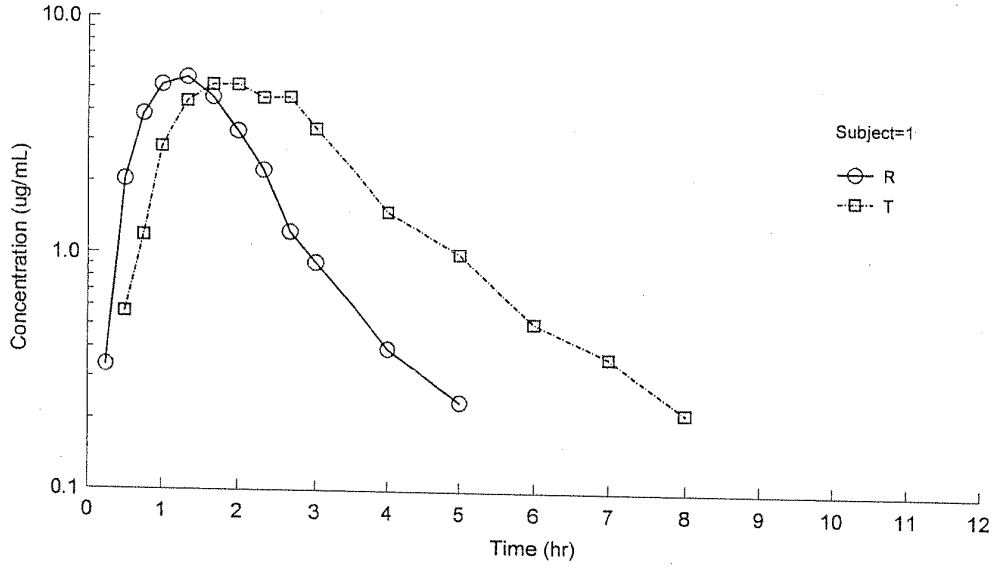
FIGURE 3 and 4
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time

(Subjects 1 and 2)



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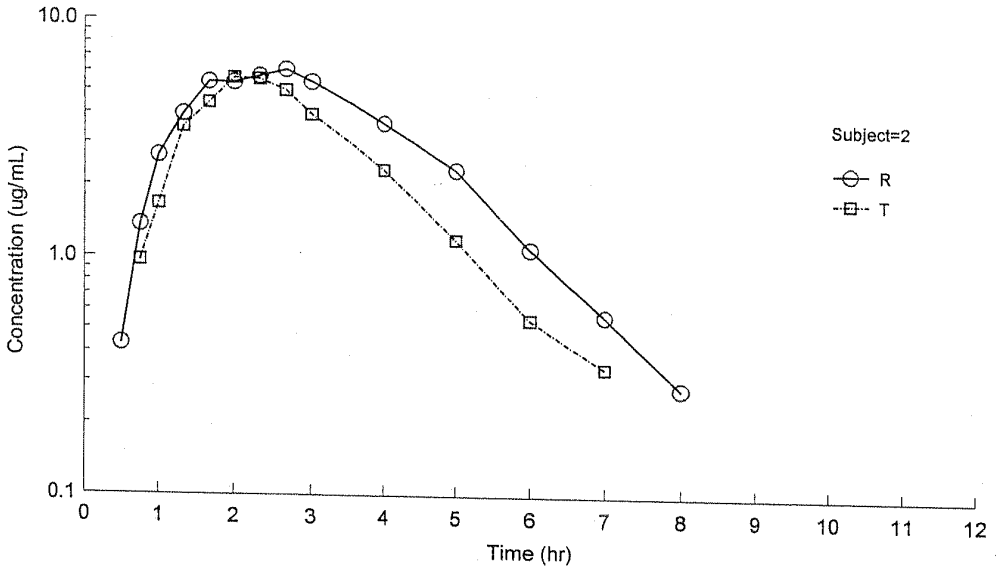

User Chart
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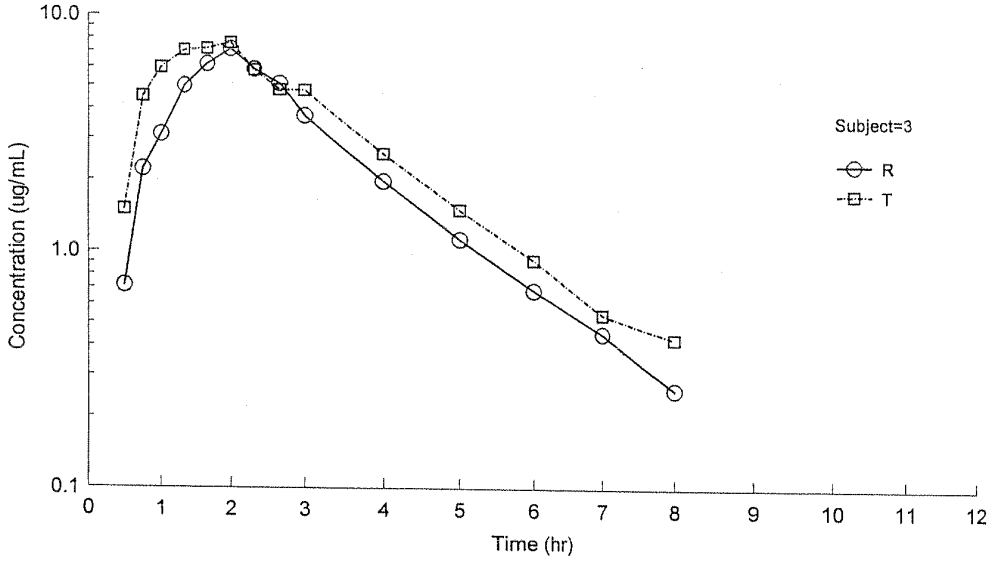
FIGURE 5 and 6
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time

(Subjects 3 and 4)



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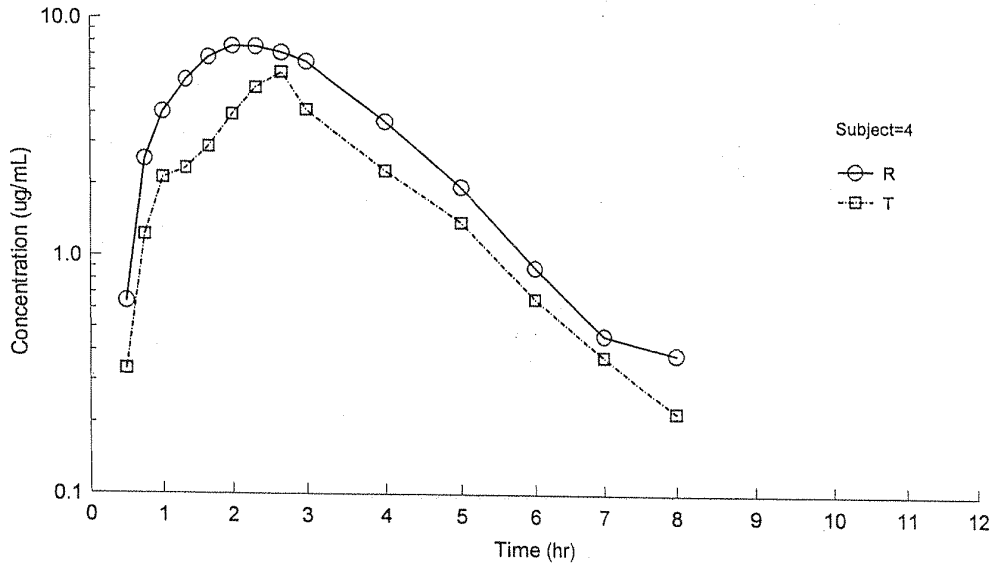

User Chart
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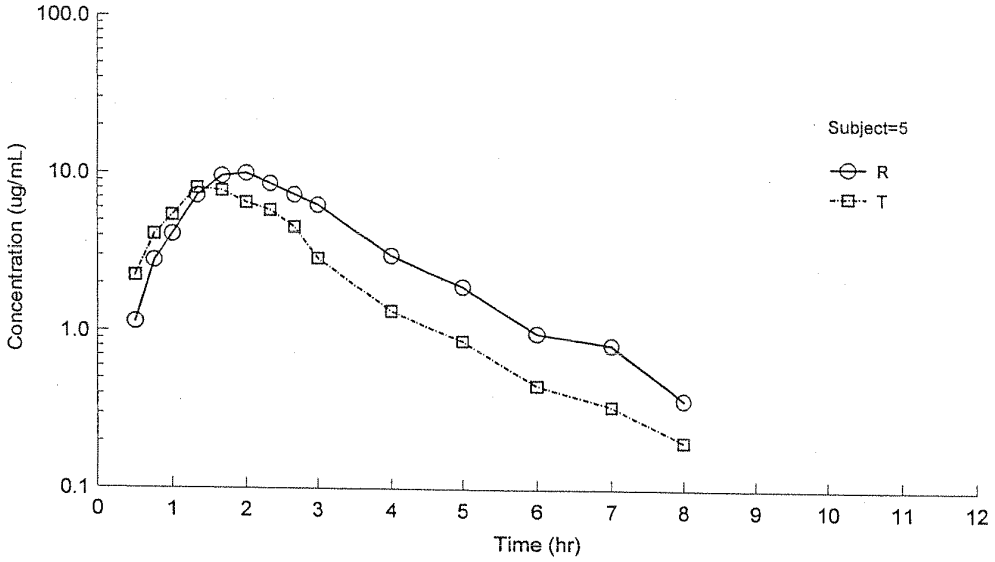
FIGURE 7 and 8
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 5 and 6)



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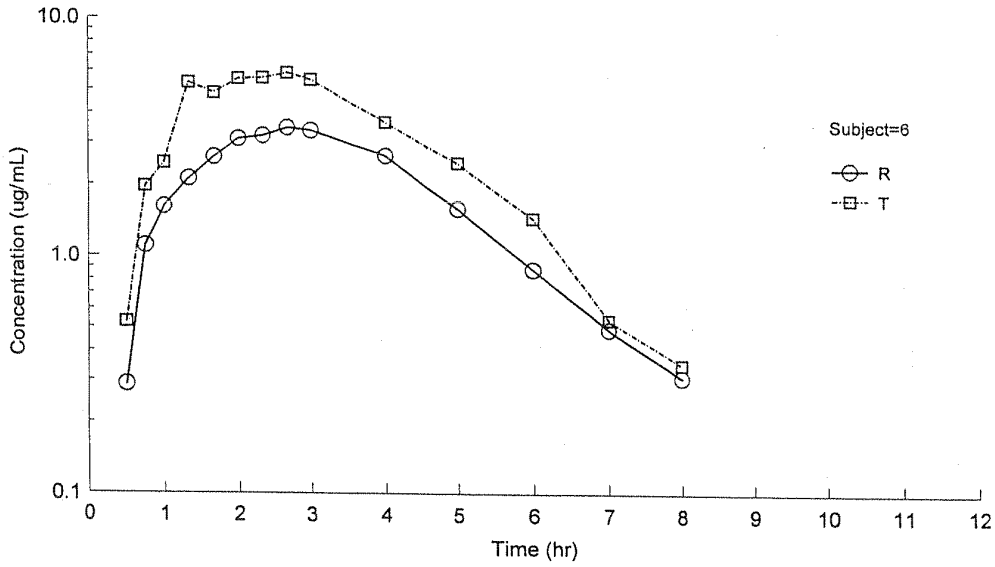
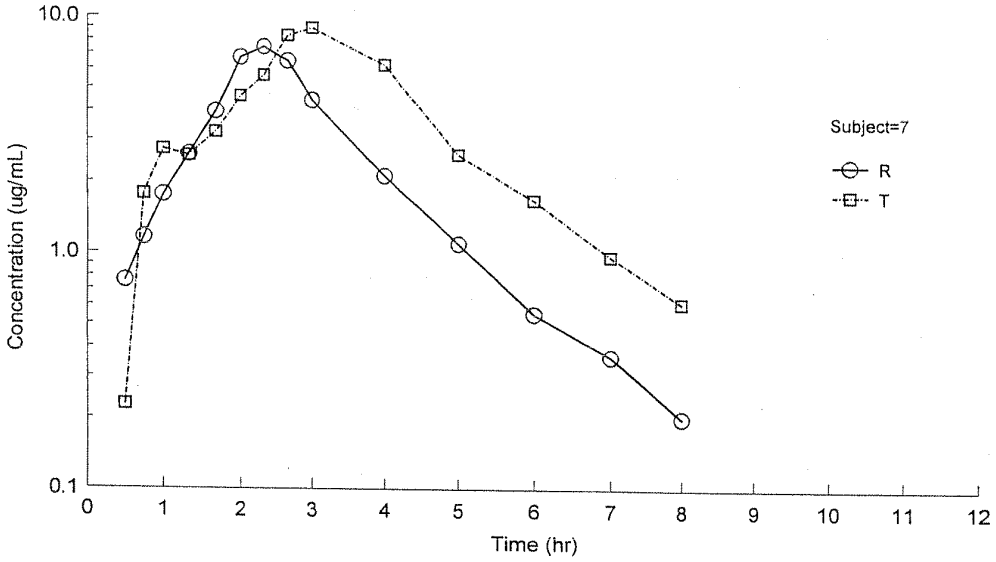


User Chart
C:\CPD-BE\Amoxicillin\Amx0604\ind semi log plots.pco (14-Feb-2005)

FIGURE 9 and 10
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 7 and 8)



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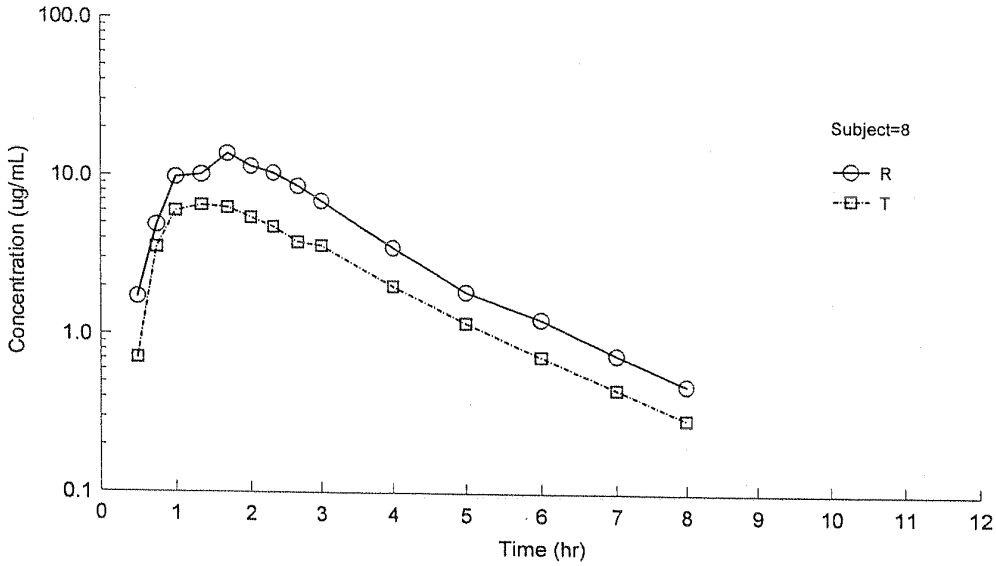

User Chart
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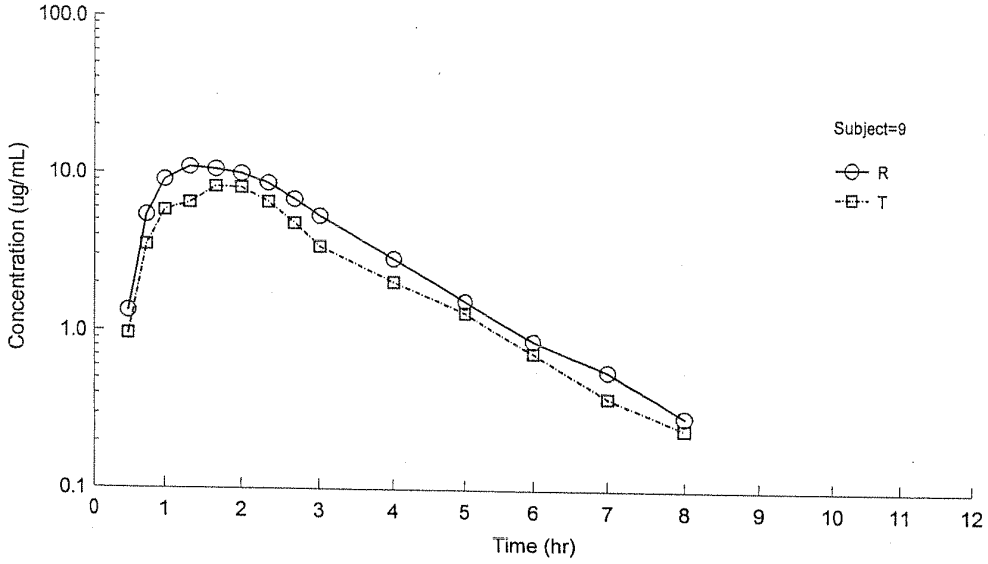
FIGURE 11 and 12
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 09 and 10)



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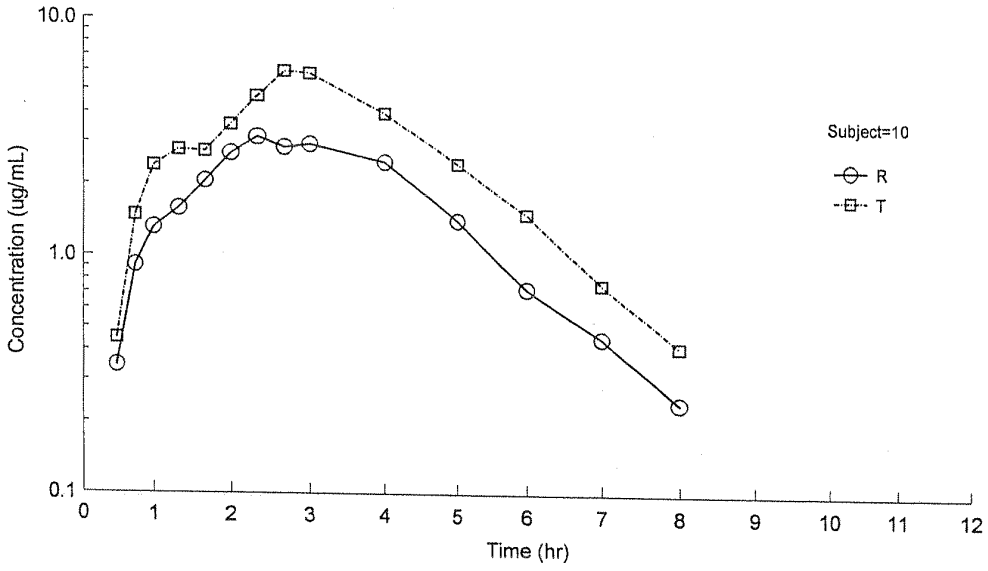

User Chart
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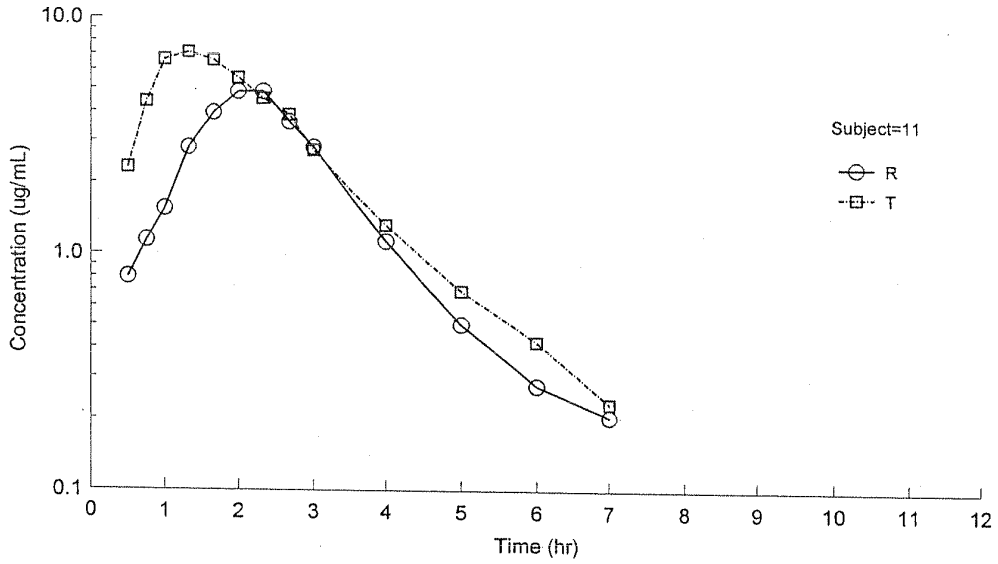
FIGURE 13 and 14
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 11 and 12)



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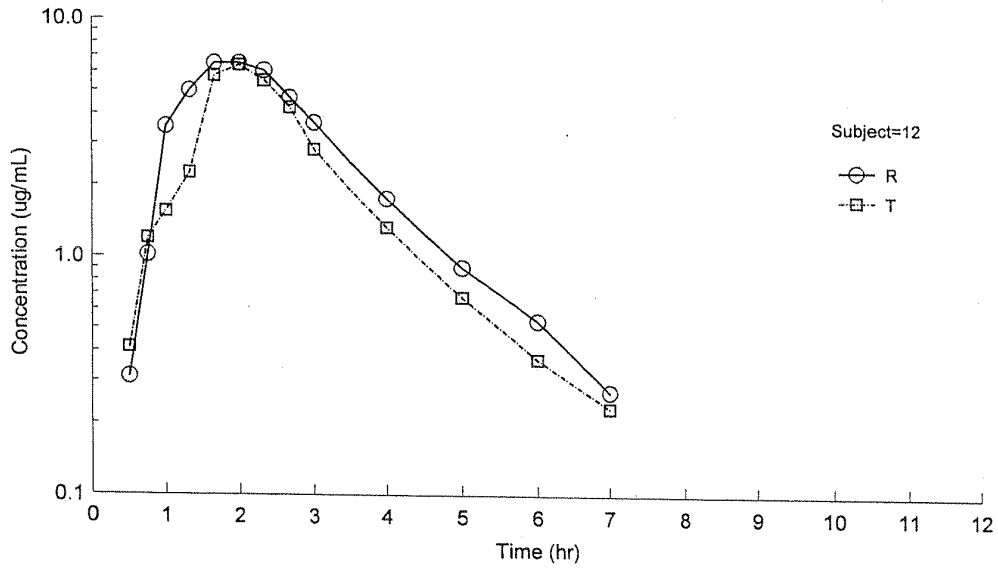
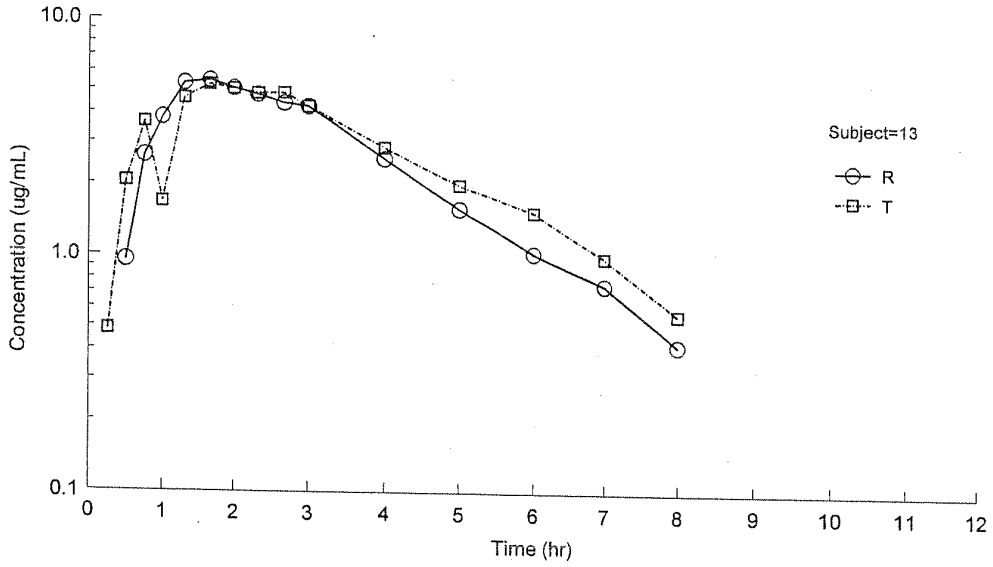


User Chart
C:\CPD-BE\Amoxicillin\Amx0604\ind semi log plots.pco (14-Feb-2005)

FIGURE 15 and 16
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 13 and 14)



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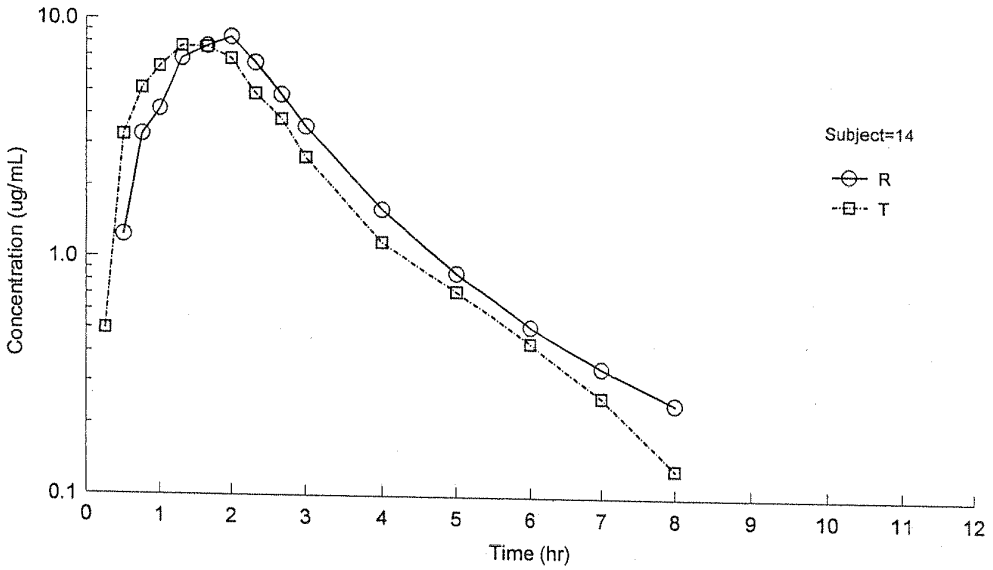
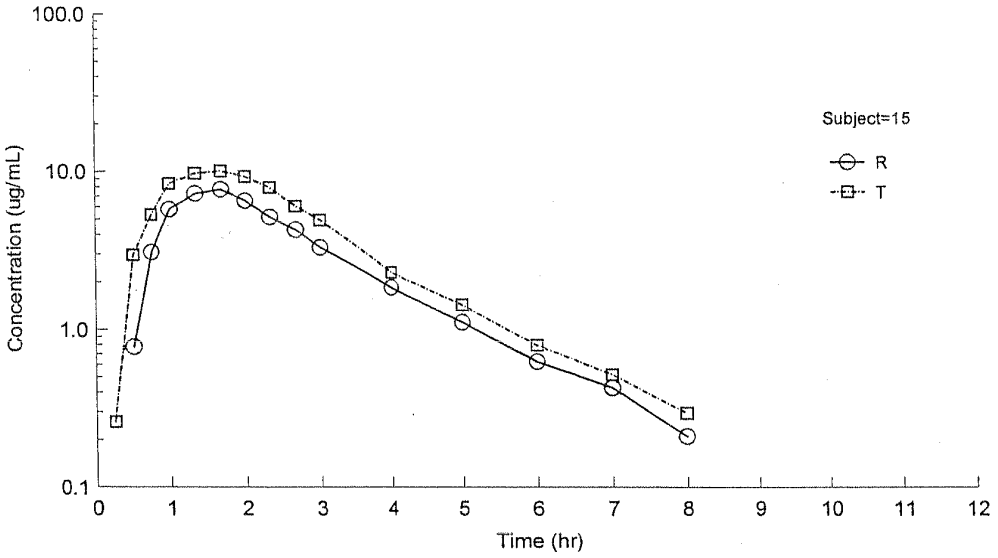


User Chart
C:\CPD-BE\Amoxicillin\Amx0604\ind semi log plots.pco (14-Feb-2005)

FIGURE 17 and 18
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time

(Subjects 15 and 16)



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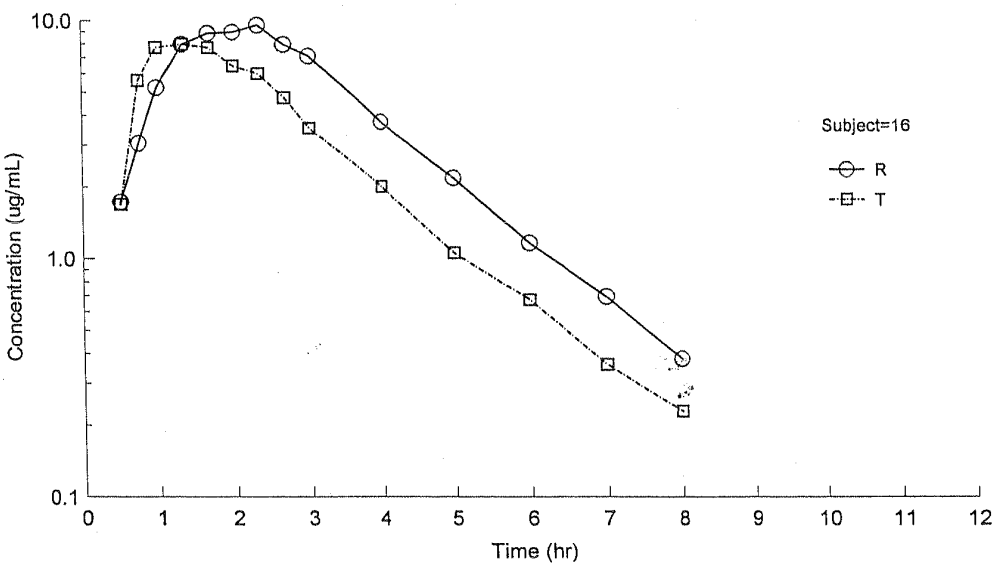
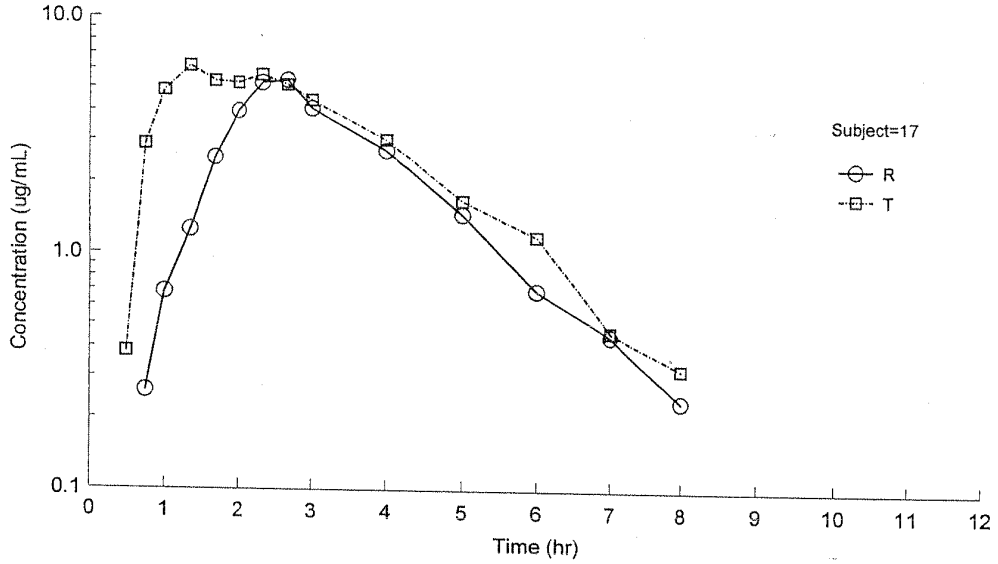


User Chart
C:\CPD-BE\Amoxicillin\Amx0604\ind semi log plots.pco (14-Feb-2005)

FIGURE 19 and 20
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 17 and 18)



User Chart
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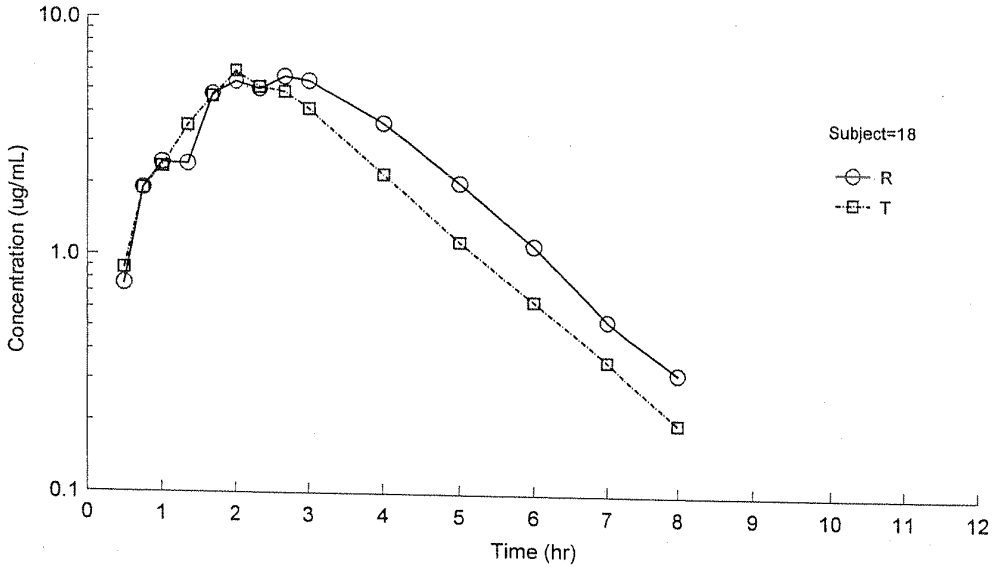

User Chart
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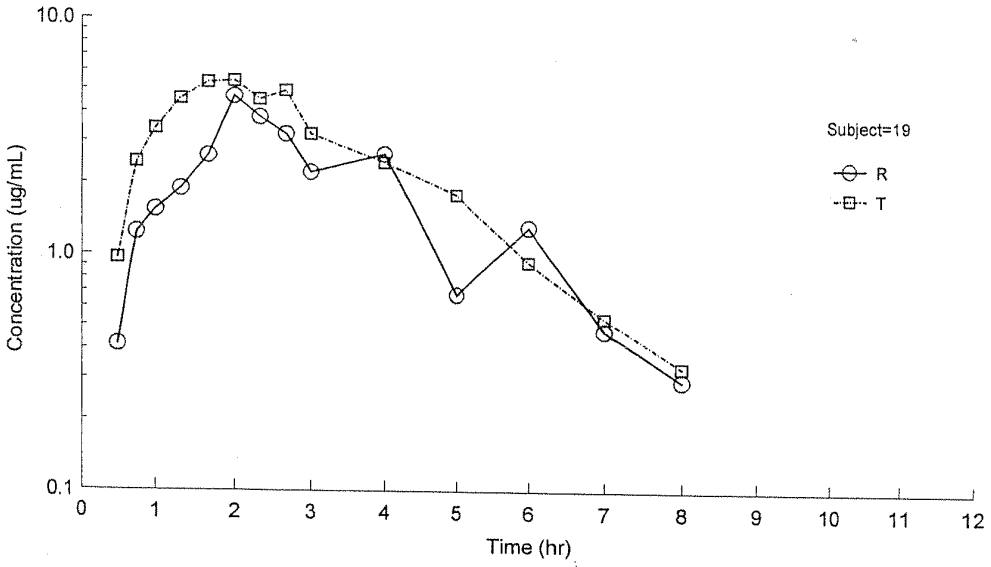
FIGURE 21 and 22
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 19 and 20)



User Chart
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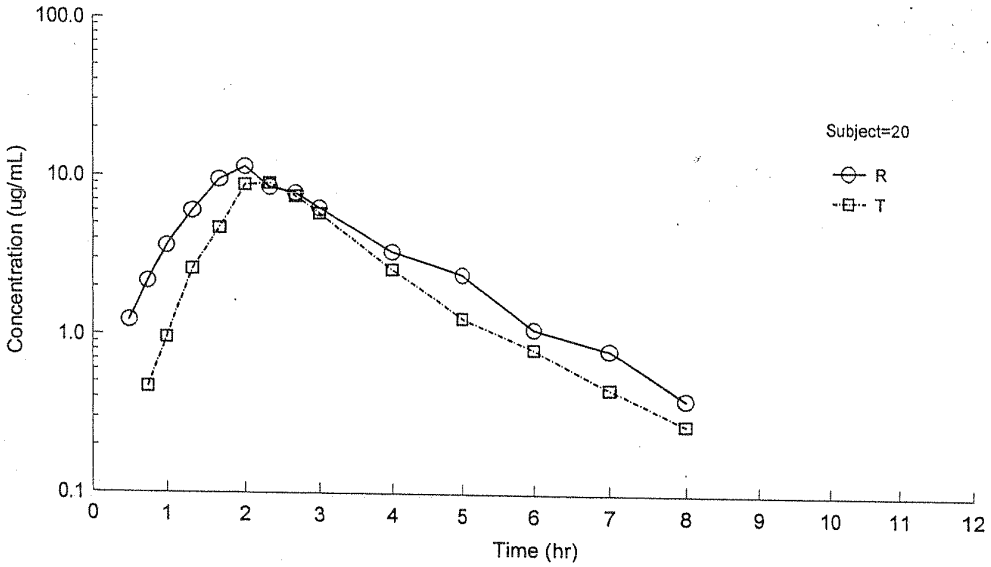

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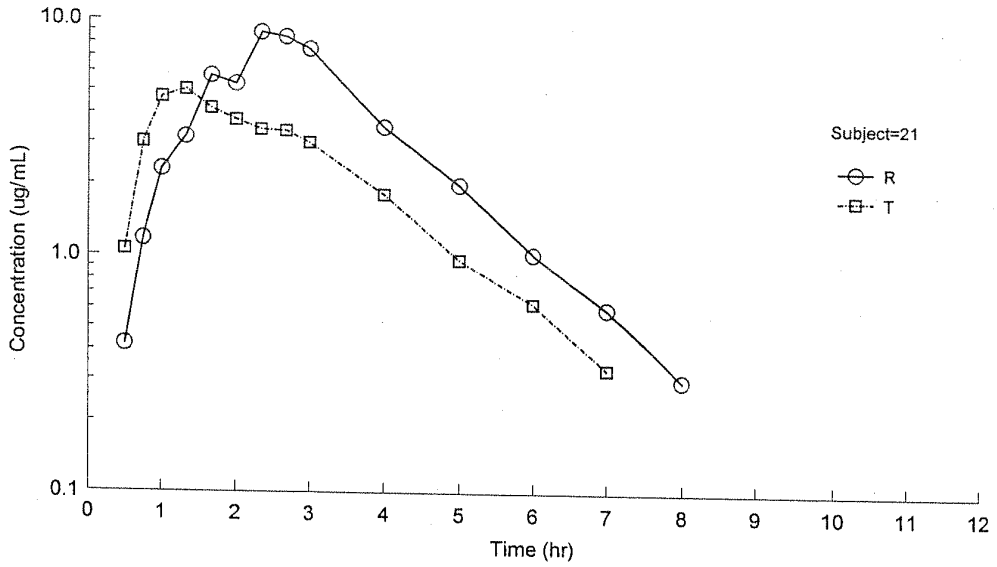
FIGURE 23 and 24
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time
(Subjects 21 and 22)



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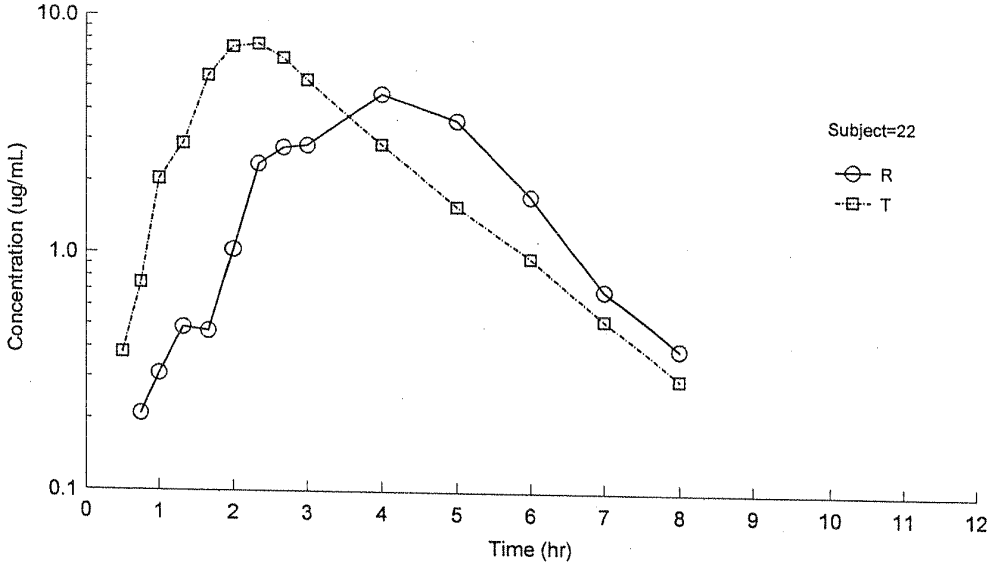

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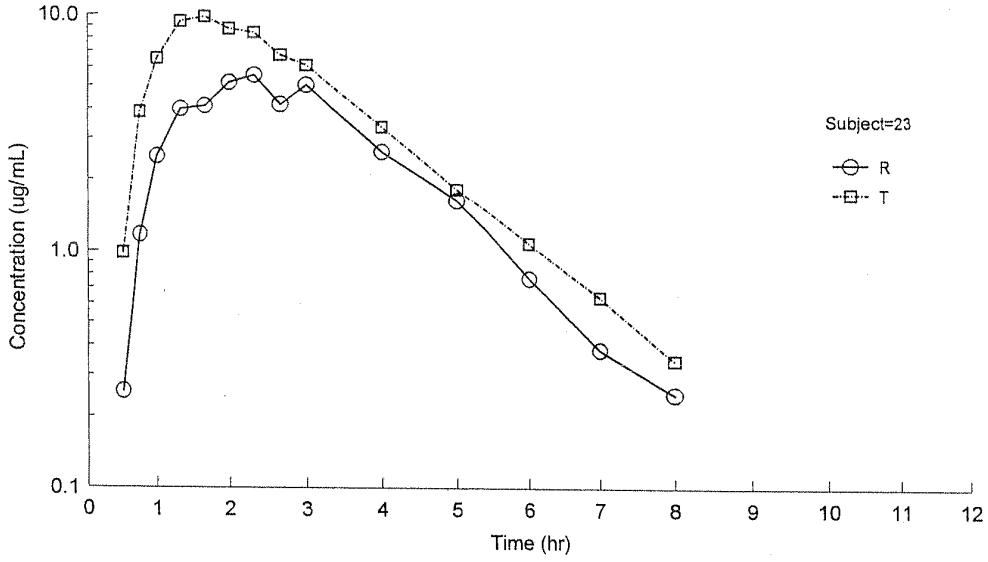
FIGURE 25 and 26
Semi-log Individual Subject Plasma Amoxicillin Concentrations Versus Time

(Subjects 23 and 24)



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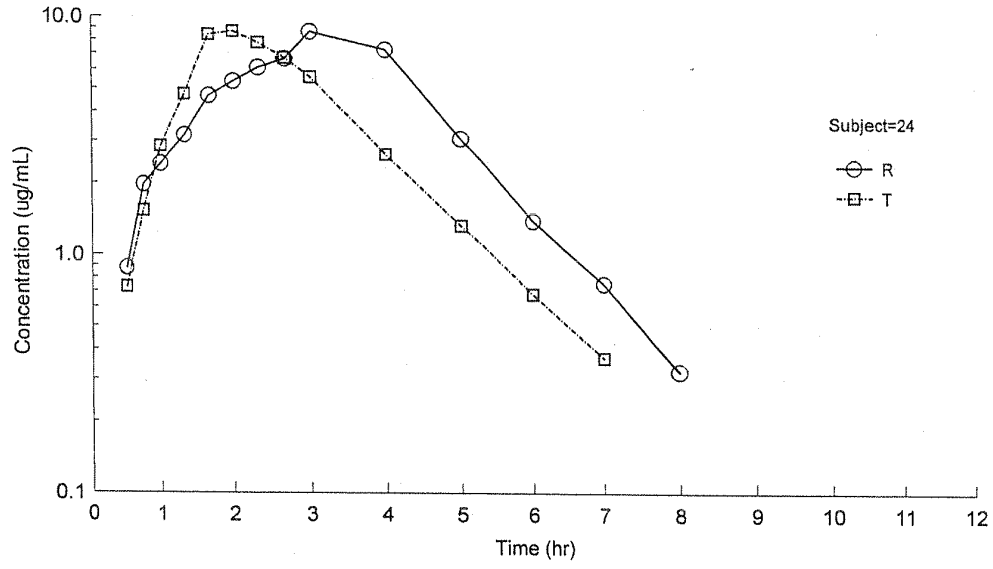

User Chart
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19.0 List Of Annexures

(i) Protocol for study No Amx-06/04

(ii) Informed Consent Document For Study No: Amx-06/04 (Telugu and English version)

(iii) Randomization Schedule

APL INSTITUTIONAL REVIEW BOARD (APL-IRB)

APL-IRB-219/04
Date: November 02nd, 2004

To

The Principal Investigator
Clinical Pharmacology Department
APL Research Centre
Survey No.313, Bachupally Village
Quthubullapur Mandal
R.R. District – 500 072.

Sub: Decision of APL-IRB for expedited approval on BA research with Study No. Amx-06/04

Ref: Your Letter No. CPD/336/04 dated November 02nd, 2004 and other relevant documents.

Dear Sir,

With reference to your above mentioned letter and after reviewing the enclosed final Protocol and Informed Consent documents, IRB is pleased to grant expedited approval for conducting the study titled, **"An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules (Test) of Aurobindo Pharma Ltd., India and Amoxil (Reference) capsules of GlaxoSmithkline, UK, in 24 healthy, adult, male, human subjects under fasting conditions."** as per ICH-GCP / GLP guidelines.

Sincerely yours,

Chairman
APL-IRB

APL Institutional Review Board (APL-IRB) Date 02/11/04

STUDY PROTOCOL

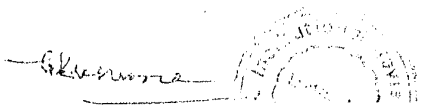
An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules (Test) of Aurobindo Pharma Ltd., India and Amoxil (Reference) capsules of GlaxoSmithkline, UK, in 24 healthy, adult, male, human subjects under fasting conditions.

Study No. Amx-06/04
Date: 16th October, 2004

Reference (R): Amoxil capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin, manufactured by GlaxoSmithkline, UK.

Test (T) : Amoxicillin capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin, manufactured by Aurobindo Pharma Ltd., India.

Clinical Pharmacology Department
APL Research Centre
Survey No. 313, Bachupally Village
Quthubullapur Mandal
Hyderabad– 500 072
India.



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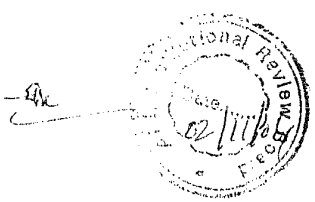

1.0 ABBREVIATIONS

APL-CPD	:	Aurobindo Pharma Limited – Clinical Pharmacology Department
Approx.	:	Approximately
AUC	:	Area under curve
AST	:	Aspartate Transaminase
ALT	:	Alanine Transaminase
BE	:	Bioequivalence
BP	:	Blood Pressure
BMI	:	Body Mass Index
CV	:	Coefficient of Variation
COA	:	Certificate of Analysis
CCF	:	Congestive Cardiac Failure
CPD	:	Clinical Pharmacology Department
CUE	:	Complete Urine Examination
ECG	:	Electro Cardiogram
EDTA	:	Ethylene Diamine Tetra Aceticacid
FRD	:	Formulation Research Development
γ-GT	:	Gama Glutamyl Transpeptidase
HBV	:	Hepatitis B Virus
HBs(Ag)	:	Hepatitis B surface Antigen
HCV	:	Hepatitis C Virus
LC-MS-MS	:	Liquid Chromatography Mass Tandem Spectroscopy.
HIV	:	Human Immunodeficiency Virus
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonisation
IRB	:	Institutional Review Board
K.cal	:	Kilo calories
LFT	:	Liver function tests
Ltd	:	Limited
L/h	:	Litres per hour
LOQ	:	Limit of Quantification
mcg	:	Microgram
PA	:	Posterior-Anterior View
QAD	:	Quality Assurance Department
R	:	Reference
RPR	:	Rapid Plasma Reagin
RFT	:	Renal function tests
RCF	:	Relative Centrifugal Force
SGOT	:	Serum Glutamate Oxaloacetate Transaminase
SGPT	:	Serum Glutamate Pyruvate Transaminase
SOP	:	Standard Operating Procedure
SAS	:	Statistical Analysis System
T	:	Test
XX	:	Current Version Number of SOP

2.0 PROTOCOL SUMMARY

Study Objective	To compare the rate and extent of absorption of Amoxicillin capsules (Test) of Aurobindo Pharma Ltd., India with that of Amoxil capsules (Reference) of GlaxoSmithkline, UK, when given in equal doses of single oral dose containing 500 mg of Amoxicillin in 24 healthy, adult, male, human subjects under fasting conditions.
Introduction	Amoxicillin is a semisynthetic antibiotic. It is an analog of ampicillin, with a broad-spectrum bactericidal activity against many gram-positive and gram-negative microorganisms. It is more rapidly and more completely absorbed than ampiciliin when given by mouth. It is used to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.
Drug Products	Reference(R): Amoxil capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin. Mfg. By: GlaxoSmithkline, UK. Test (T): Amoxicillin capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin. Mfg. By: Aurobindo Pharma Ltd., India The Lot No, Mfg. Date and Exp. Date for both Test and Reference products will be included in the Summary report.
Dosing	A single oral dose of 500 mg x 1 capsule of reference (R) or test (T) will be administered as per the randomization schedule. Subjects will receive the alternate treatment in the subsequent period following crossover with the following treatment sequence i.e. R–T or T–R. Subjects will be dosed with 240 mL of drinking water after an overnight fasting of atleast 10 hours.
Study Design	Open label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules in 24 healthy, adult, male, human subjects under fasting conditions.
Number of Subjects	24+ 4 (standby)

Dietary Plan	Subjects will be provided standard meal (dinner) consisting of approx. 1000 Kcal during the day of check-in (Day–0). Subjects will be required to fast overnight (atleast 10 hours) before dosing and minimum of 4 hours thereafter. Post dose meal on Day –1(Dosing Day) consisting of approx. 1300 Kcal as per the meal plan provided by dietician (divided into lunch-approx. 900 Kcal., and snacks- approx.400 Kcal will be provided at 4.0 hours 15 minutes (lunch), and 8.0 hours 30 minutes (snacks) respectively. During clinical residence, the meal plans will be kept identical for both periods. Information on the standardized meal, quantity and time will be recorded on the relevant raw data forms. Drinking water will not be permitted one hour before dosing and until one hour post-dose, at other times drinking water will be permitted *ad libitum*.
Screening	Volunteers aged from 18 to 50 years with a body mass index (BMI) within 19-26 will be selected according to the inclusion and exclusion criteria. They will be healthy according to physical examination (including vital signs) and laboratory test results {(hematological investigations, biochemistry, urinalysis, 12-lead ECG and chest X-ray (PA view)} including negative HIV, HBs(Ag), Hepatitis C and RPR tests as well as negative screening for drugs of abuse (barbiturates, Benzodiazepines, Opioids, Amphetamines and Cannabinoids) in urine. Screening for drugs of abuse in urine will be tested during pre-study screening and during the day of check-in for Period-I&II. However Screening for drugs of abuse (barbiturates, Benzodiazepines, Opioids, Amphetamines and Cannabinoids) in urine will be done only once if the volunteer is screened on the day of check-in for Period-I.
Sampling Schedules	Blood samples 1 x 6 mL will be collected in prelabelled vacutainer tubes containing potassium EDTA during each period. The venous blood samples will be withdrawn pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 12.0 hours post-dose.
Blood Loss	For each subject the total number of blood draws will be 34 (17x2 for both the periods). The total volume of blood withdrawn will be 254 mL. (Approx. 9 mL for screening, 34 mL discarded heparinised blood, 204 mL for both the periods and 7 mL for post study laboratory tests at the end of Period-II at the time of cl

Washout Period	There will be a washout period of atleast 7 days between the two treatment schedules.
Safety Assessments	In each period, vital signs monitoring will be done at the time of volunteer check-in (16.30-21.15 hours), pre-dose and at 1.0, and 12.0 hours post-dose. Adverse event monitoring will be done at 3.0 and 8.0 hours post-dose and if any adverse events are observed by either clinical staff or reported by subjects at times other than scheduled times will be recorded.
Clinical Residence	Atleast 10.0 hours 45 minutes before dosing and until the 12.0 hour blood draw in each period.
Post-study Lab Investigations	7 mL blood will be collected for post-study laboratory investigations (Hematological investigations including absolute eosinophil count, LFT and RFT) at the time of 12.0 hour blood sample collection in Period-II or at any stage after the dosing if the subject is withdrawn or dropped from the study for any reason.12-lead ECG and skin examination for Maculopapular rash will also be done at the end of 12.0 hour blood sample collection of Period-II or at the time when subject is withdrawn/dropped from the study.
Bioanalytical Method and Analytical Procedure	Amoxicillin will be estimated in plasma using a validated LC-MS-MS method. Reanalysis will be performed as per the SOP No: APL-CPD-423-XX of the bioanalytical unit.
Pharmacokinetic Parameters and Analysis	T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, k_{el} and $T_{1/2}$ will be determined from the plasma Amoxicillin data using WinNonlin version 3.3.
Statistical Analysis	Summary statistics, ANOVA, 90% confidence interval and Ratio Analysis, intra subject variability will be calculated using SAS 8.2 version.
Ethical Considerations	The study will be carried out as per the ICH-GCP guidelines and principles of Declaration of Helsinki. Protocol and ICF document approval will be taken from the IRB before initiation of the study.
Summary and Final Report	Summary and final report will be prepared having clinical, bioanalytical, pharmacokinetic and statistical data subjected to Quality Audit
Archives	Raw data and reports will be archived at the CPD-APL Research Centre with controlled access, for 15 years.

3.0 INVESTIGATOR'S DECLARATION

Study Title: An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules (Test) of Aurobindo Pharma Ltd., India and Amoxil (Reference) of GlaxoSmithkline, UK, in 24 healthy, adult, male, human subjects under fasting conditions.

We, the undersigned, declare that we have read and understood this protocol and hereby agree to conduct the study in accordance with all requirements regarding the obligations of investigators and all other pertinent requirements of the ICH 'Guideline for Good Clinical Practice' and 'Good Laboratory Practice'. We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

We agree to comply with all relevant Standard Operating Procedures (SOPs) required for the conduct of this study and would document any significant deviation occurring during the study.

Principal Investigator
(Mr. N.Nagaraj Kumar)

02/11/04
Date

Clinical Investigator
(Dr. Nitin Kulkarni)

02/11/04
Date

Bioanalytical Investigator
(Mr. Avinash. B. Gaikwad)

02/11/04
Date

Statistical Investigator
(Mr.P. Pramod Kumar Reddy)

02/11/04
Date

4.0 CONTACT PERSONNEL

Principal Investigator : Name: Mr. N. Nagaraj Kumar
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Telephone: 91-40-23040261, 91-40-23040262

Clinical Investigator: Name: Dr. Nitin Kulkarni
Address: Clinical Unit
Clinical Pharmacology Department
APL Research Centre
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2nd & 3rd Floor of Mirra Multispeciality
Hospital, Alluri Sitaramaraju Nagar
Opp. J.P.N.Nagar Colony, Miyapur
Hyderabad-500 050
India.

Telephone: 91-40-23045809, 91-40-23045709

Chairman APL IRB : Name : Justice Y.V. Narayana (Retd.)

Address : Flat No: 402 Pooja's Pride
Plot No: 75, Srinagar Colony
Hyderabad-500 073,
India.

Telephone: 91-40-23743173.

5.0 FACILITIES

5.1 Clinical Unit
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2nd and 3rd Floor, Mirra Multi-Speciality Hospital
Alluri Sitaramaraju Nagar, Opp. J.P.N.Nagar Colony, Miyapur
Hyderabad – 500 050, India.

5.2 Clinical Investigations Unit

Clinical Pharmacology Department
APL Research Centre
Plot Nos. 33 – 35
2nd Floor, Mirra Multi-Speciality Hospital
Alluri Sitaramaraju Nagar,
Opp. J.P.N.Nagar Colony,
Miyapur, Hyderabad – 500 050,
India.

5.3 Bioanalytical Unit
Clinical Pharmacology Department
APL Research Centre
Survey No. 313
Bachupally Village
Quthubullapur Mandal
Hyderabad – 500 072, India.

5.4 Pharmacokinetic & Biostatistical Unit
Clinical Pharmacology Department
APL Research Centre
Survey No. 313,
Bachupally Village
Quthubullapur Mandal
Hyderabad – 500 072, India.

5.5 Biomedical Waste
Medicare Incin Pvt. Ltd.
6-3-1089/G/10 & 11, Gulmohar Avenue
Rajbhavan Road, Somajiguda
Hyderabad, India.

6.0 INTRODUCTION AND INFORMATION ON REFERENCE PRODUCT

6.1 Background Information

The present study is undertaken to compare the rate and extent of absorption of Amoxicillin capsules of Aurobindo Pharma Ltd., India with that of Amoxil capsules of GlaxoSmithkline, UK when both are given as single oral dose.

6.2 Pharmacology

Amoxicillin is a semisynthetic antibiotic. It is an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. It is more rapidly and more completely absorbed than ampicillin when given by mouth. It is used to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Mechanism of Action
Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide.

6.3 Pharmacokinetics

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of cerebrospinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. In blood serum, amoxicillin is approximately 20% protein-bound. Orally administered doses of 250-mg and 875 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 mcg/mL to 5.0 mcg/mL and 5.5 mcg/mL to 7.5 mcg/mL, respectively. Hepatic metabolism is a relatively unimportant route of amoxicillin elimination. A small amount (10-20%) of the drug is metabolized by hydrolysis of the β-lactam ring to penicilloic acid.
Most of the amoxicillin is excreted unchanged in the urine. Elimination of Amoxicillin occurs via the kidneys by glomerular filtration and tubular secretion. Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin.

6.4 Interactions

6.4.1 Food Interactions

Food has no significant influence on the absorption of Amoxicillin.

6.4.2 Drug / Laboratory Test Interactions:

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using CLINITEST®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX®) be used. Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

6.4.3 Drug / Drug Interactions

- Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.
- Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated in vitro; however, the clinical significance of this interaction is not well documented.
- In common with other broad spectrum antibiotics, amoxicillin may reduce the efficacy of oral contraceptives.
- Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of toxic allergic skin reactions.
- Prolongation of prothrombin time has been reported rarely in patients receiving amoxycillin.

6.5 Adverse Reactions

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of amoxicillin:

Gastrointestinal: Nausea, vomiting, diarrhea (5%), and hemorrhagic and pseudomembranous colitis

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported.
Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic [illegible], leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions

are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, and/or dizziness have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients.

6.6 Warnings

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and appropriate therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. studies indicate that a toxin produced by *clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *c. difficile* colitis.

6.7 Precautions

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

6.8 Contra-Indications

- A history of allergic reaction to any of the penicillins is a contraindication.
- Glandular fever and lymphatic lymhoma
- Bacterial Resistance

6.9 Indications

Amoxicillin is indicated in the treatment of infections due to susceptible (only ß-lactamase negative) strains of the microorganisms in the conditions listed below:

- Treatment of urinary tract infections
- Treatment of otitis media
- Treatment of Respiratory tract infections
- Treatment of Gram-negative septicemia/infections
- Treatment of other surgical infections
- Treatment of gonorrhea
- Treatment and prevention of infective endocarditis
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence
- Typhoid and paratyphoid fever
- Skin and soft tissue infections
- Dental abscess (as an adjunct to surgical management)

7.0 STUDY OBJECTIVE

To compare the rate and extent of absorption of Amoxicillin capsules (Test) of Aurobindo Pharma Ltd., India with that of Amoxil (Reference) capsules of GlaxoSmithkline, UK, when given in equal doses of single oral dose containing 500 mg of Amoxicillin in 24 healthy, adult, male, human subjects under fasting conditions.

Reference and test product for the study are:

Reference (R): Amoxil capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin, manufactured by GlaxoSmithkline, UK.

Test (T) : Amoxicillin capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin, manufactured by Aurobindo Pharma Ltd., India.

The Lot No, Mfg. Date and Exp. Date for both Test and Reference products will be included in the Summary report.

8.0 STUDY DESIGN

8.1 Design

Open label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules in 24 healthy, adult, male, human subjects under fasting condition.

8.2 Randomization

The order of receiving the test and reference product for each subject during the two periods of the study will be determined according to randomization schedule (generated using SAS version 8.2). The randomization will be balanced and the code will be kept under controlled access. The personnel involved in dispensing of study drugs will be accountable for ensuring compliance to randomization schedule.

8.3 Number of subjects

Sufficient number of healthy, adult, male, human subjects will be screened with volunteer's consent to enroll 24 + 4 (standby) subjects for the study. All the samples from a maximum of 24 subjects completing both the study periods would be analysed. Dropouts will be replaced with the standby subjects prior to analysis. If necessary, an unequal number of subjects per period will be used.

8.4 Washout Period

Atleast 7 days washout period will be observed between two treatment schedules.

8.5 Drug Receipt, Accountability and Storage

An adequate number of drug products for administration and sample retention purpose along with the COA and *in-vitro* dissolution data, will be received by the Clinical Investigator or his designate from the concerned person of FRD. The drug products will be stored in the pharmacy under prescribed storage conditions and will be logged-in the Drug Accountability Log Book.

8.6 Drug Dispensing

The Clinical Investigator or Pharmacist will use required number of drug products based on total number of study subjects to conduct each period of the study. Remaining drug products will be stored in their original container as retention samples. The issued capsules will be transferred to the drug-dispensing containers as unit doses. The drug dispensing containers used for dispensing will be properly labeled for the study number, period number, subject number and date.

02/11/11.

8.7 Dietary Plan

Subjects will be provided standard meal (dinner) consisting of approx. 1000 Kcal during the day of check-in (Day–0).

Subjects will be required to fast overnight (at least 10 hours) before dosing and minimum of 4 hours thereafter. Post dose meal on Day –1(Dosing Day) consisting of approx. 1300 Kcal as per the meal plan provided by dietician (divided into lunch- approx. 900 Kcal., and snacks- approx. 400 Kcal will be provided at 4.0 hours 15 minutes (lunch), and 8.0 hours 30 minutes (snacks) respectively.

During clinical residence, the meal plans will be kept identical for both periods. Information on the standardized meal, quantity and time will be recorded on the relevant raw data forms.

Drinking water will not be permitted one hour before dosing and until one hour post-dose, at other times drinking water will be permitted *ad libitum*.

8.8 Study Termination

The Principal Investigator/ Clinical Investigator reserves the right to terminate the study at any time for safety reasons or in the best interest of the subject's welfare. The IRB can also cancel the study for major ethical violations. The subjects would be briefed on the reasons for the termination and compensated adequately.

9.0 SUBJECT SELECTION, MONITORING AND ASSESSMENT

9.1 Eligibility Assessment

For the purpose of this study the following eligibility assessments will be carried out before enrolment of any volunteer into dosing / sampling phase of the study :

9.1.1 Screening

The screening will be carried out after taking a written informed consent for screening from volunteers and will include the following:

- Demographic data including name, sex, date of birth, height and weight, BMI, history of smoking, history of intake of abusive/recreational drugs, history of alcohol consumption, history of blood donation, history of participation in a drug research study.
- Medical history including present complaints (if any), relevant past medical history, family history, history of any allergy to food, drugs, animals and treatment history.
- Complete physical examination including vital signs (Blood Pressure, Pulse rate, Oral temperature and Respiratory rate) and Systemic examination.
- 12-lead ECG for heart rate, rhythm and specific finding (if any).
- Chest X-ray (PA view).

9.1.2 Clinical laboratory tests

- Hematological investigations–RBC count, Platelet count, Hemoglobin, Total and differential WBC count.
- Blood grouping & Rh typing and bleeding time.
- Biochemistry – Fasting blood glucose, serum sodium, potassium, chloride, calcium, phosphorous and total cholesterol.
- Hepatic profile – SGOT, SGPT, & Total Bilirubin, Alkaline Phosphatase, γ – GT, total protein and albumin.
- Renal profile – serum creatinine, serum urea and serum uric acid.
- Urine – Complete Urine examination, which include physical, bio-chemical and microscopic examination. Drugs of abuse (Benzodiazepines, Opioids, Amphetamine, Cannabinoids and Barbiturates).
- Screening for infectious diseases – HIV 1 & 2, HBs(Ag), HCV and RPR.

9.2 Inclusion Criteria

- Healthy males within the age range of 18 to 50 years.
- Have a body mass index within 19-26.
- Willingness to provide written informed consent to participate in the study.
- Absence of disease markers of HIV 1 & 2, hepatitis B & C virus and RPR.
- Absence of significant disease or clinically significant abnormal laboratory values on laboratory evaluation, medical history or physical examination during the screening.
- Have a normal 12-lead ECG.
- Have a normal chest X-ray (PA view).
- Comprehension of the nature and purpose of the study and compliance with the requirement of the entire protocol.
- Have no history or evidence of allergy or hypersensitivity to Amoxicillin and other penicillins and Cephalosporins.
- Have no history of significant systemic diseases.
- Have no history of psychiatric disorders.
- No donation of blood (one unit or 3[illegible] /s prior to receiving the first dose of study medication.

- No history of addiction to any recreational drug or drug dependence.
- No participation in any clinical study within the past 56 days.
- No receipt of any prescription drugs (eg: probenecid and allopurinol) or over-the-counter drugs (e.g. Cold preparations, antacid preparations, vitamins and natural products used for therapeutic benefits), within two weeks prior to receiving the first dose of study medication
- No history of dehydration from diarrhea, vomiting or any other reason within a period of 24 hours prior to the study.
- No family history of neurological disorders.
- Have not taken any medication until last blood sampling time point of period-II without investigator(s) consent.
- Have negative results for drugs of abuse in urine during pre-study screening and during the day of check-in for Period-I & II.
- No history of malaria and absence of psoriasis.

9.3 Exclusion Criteria

- History of seizure.
- History of alcohol consumption for more than two units/day (1 unit = 30 ml of spirit/or 1 pint of beer), or having consumed alcohol within 48 hours prior to dosing.
- High caffeine (more than 5 cups of coffee or tea/day) or tobacco (more than 9 cigarettes/beedies/cigars per day) consumption.
- History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.
- Receipt of any prescription drug therapy or over-the-counter (OTC) drugs (eg: probenecid and allopurinol) within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks which is likely to affect the hepatic biotransformation (e.g. barbiturates, rifampicin etc.).
- An unusual or abnormal diet, for whatever reason e.g. because of fasting due to religious reasons.

9.4 Withdrawal Criteria

Subjects may be withdrawn from the study by the Investigator(s) for any of the following reasons during the course of the study:

- If the subject suffers from significant illness.
- After dosing, if the subject vomits, at or before 2 times the median T_{max} of Amoxicillin, subject will be withdrawn from study.
- If the subject requires unacceptable concomitant medications.
- If the subject missed, a minimum of 3 sampling time points in terminal phase and the subject missed a last sampling time point.
- If the subject has entered the study in violation of the inclusion and the exclusion criteria.
- If the subject is found to be non co-operative.
- If the subject decides to voluntarily withdraw from the study.

Note:

Any subject withdrawals will be reported for :

- Reasons for withdrawal (if any).
- Clinical assessment of the subject will be done at the time of withdrawal, if a subject withdraws during the residential stay at Clinical Unit of APL-CPD.

9.5 Dosing and Treatment

A single oral dose of 500 mg x 1 capsule of reference (R) or test (T) product will be administered along with 240 mL water as per the randomization schedule in the presence of Clinical Investigator or his designate. Subjects will receive the alternate treatments in the subsequent periods after crossover with the following possible treatment sequence i.e. either R-T or T-R.

9.6 Assessment of Compliance

9.6.1 Dosing

Compliance for dosing after dose administration will be assessed by examination of the oral cavity by trained study personnel.

9.6.2 Concomitant Medication

The attending physician or the Clinical Investigator shall decide whether to continue with the subject in case the subject requires concomitant non-study medications during the study or the washout period. The decision will be based on the following:

- If there is likelihood of pharmacokinetic interactions with the non-study medications given during the course of the study.

- Depending on the time and duration of non-study medications.

9.6.3 Diet

- A standardized meal (Refer section 8.7, Dietary Plan) will be provided to the study subjects.
- Subjects will be instructed to abstain from alcohol and xanthine containing food and beverages, (chocolates, tea, coffee or cola drinks) cigarettes and tobacco products, for atleast 48 hours, prior to check-in, for each period and during the in-house stay.

9.6.4 Activity

Subjects will be dosed while in sitting posture and will be instructed to remain seated or ambulatory for first two hours following the drug administration. However postural change of the subjects can be allowed for performing scheduled vitals. Thereafter, the subjects will be allowed to engage only in normal activities while avoiding severe physical exertion. In case of adverse events/medical emergency, subject is allowed to lie down on the right side and those subjects will be re evaluated to find out whether they can be continued in the study.

9.6.5 Clinical Residence

Subjects will be admitted and housed in the clinical facility at least 10.0 hours 45 minutes before the administration of the dose during each period of the study. They will be discharged at the end of 12.0 hour sample collection in each period of the study, if not suffering from any adverse events. In case of any adverse events, the subjects will be kept under observation until recovery.

9.7 Blood Sampling Schedule

A total of 16 blood samples (6 ml each) in each period will be collected. The blood samples will be collected prior to administration of dose in each period (pre-dose) and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 12.0 hours post-dose. The actual collection time of each blood sample will be recorded. Time deviations will be noted as protocol deviations.

For each subject the total number of blood [redacted] mL.

9.8 Blood Sampling Procedure

Samples will be collected through an indwelling cannula placed in a forearm vein. The pre-dose samples will be collected prior to drug dosing. The post-dose samples will be collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute would be recorded. Time deviations more than 2 minutes of actual blood collection time will be recorded as protocol deviations.
Intravenous indwelling cannula would be kept in place as long as required by injecting adequate amount but not more than 1 ml of 5 IU/mL of heparin in normal saline solution during the collection of multiple samples. In such a case, the blood sample would be collected after discarding the first 1 mL of heparinised blood from the tubing. Blood may also be withdrawn by a fresh clean venipuncture either by using sterile syringe and needle or disposable sterilised needle and vacutainer if the cannula is blocked.

If the blood sample collection time coincides with the other study events like vitals, subject well-being questionnaire and meal, the sequence of the events would be followed as: blood sample collection followed by vitals, subject well-being questionnaire and meal.

9.9 Handling of Blood Samples

Each blood sample will be collected into a pre-labeled vacutainer tube containing potassium EDTA. The samples collected at each time point will be centrifuged (at 2500 RCF and 4°C for 10 minutes) to separate plasma, immediately after receiving the blood samples from all the subjects. The separated plasma samples will then be transferred to deep freezer maintained at below –20°C in pre-labeled tubes for temporary storage up to 4.0 hours and finally transferred to or directly to deep freezer maintained at below -70°C for storage until analysis. Separated plasma samples of the subjects will be transferred from Clinical Unit to Bio analytical Unit as per the SOP No:APL-CPD-228-XX.

10.0 SAFETY ASSESSMENT

Safety assessments would be carried out at the time of screening, subject check-in, during the course of the study and subject check-out by recording vital signs and adverse events monitoring (subject questionnaire) in both the periods.

Detailed medical examination including medical history, general and systemic examination, vital signs, Chest X-ray (PA view), 12-lead ECG and laboratory tests (as per Section 9.1.2 'Clinical Laboratory Tests') would be carried out at the time of screening to exclude any clinically significant medical condition that may interfere or likely to interfere with the pharmacokinetics of the drug. At the end of period-II, 12 lead ECG and laboratory tests [hematological investigations including absolute eosinophil count, RFT, LFT] and skin examinations for maculopapular rash would be carried out to rule out any significant changes from the baseline values. Whenever necessary, expert medical opinion will be t

10.1 Vital Signs

In each period, vital signs monitoring will be done at the time of check-in, pre-dose and at 1.0 and 12.0 hours post-dose.

10.2 Handling and Reporting of Adverse Events

Adverse event monitoring (subject well being questionnaire) will be done at 3.0 & 8.0 hours and if any adverse events are observed by either clinical staff or reported by subjects at times other than scheduled times will be recorded.

During the course of the study, subjects will be monitored for any adverse event, which will be recorded in the appropriate raw data forms. The subjects would be required to inform the attending personnel or physician of any adverse event that may occur during the time of their stay at the clinical facility. The attending physician/staff nurse may also enquire about any adverse events that may occur during the course of the study while monitoring the vital parameters. A medically qualified physician will be available round the clock during the time of housing at the clinical facility/or on phone. All drug and/or study related adverse events will be treated by the attending physician either at Clinical Unit, CPD or Mirra Multispeciality Hospital or tertiary Hospital at no extra cost to the subject as per SOP No.s: APL-CPD-222-XX and APL-CPD-245-XX.

Any adverse event observed shall be recorded and appropriately treated. The IRB and regulatory bodies (whenever applicable) shall be informed of the serious adverse event as necessary with in one week.

Any serious adverse events will also be reported on telephone or fax to management immediately on identification with full follow-up report to follow as soon as further information is available.
All adverse events shall be evaluated for duration, severity, action taken, date and time of resolution and association with the study treatment. The study may be suspended or terminated depending on the seriousness of the adverse event.

Note:
Adverse Drug Reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose.

An adverse event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests) or a disease temporarily associated with the use of the study medication.
A Serious Adverse Event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalisation
- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect.

Unexpected Adverse Event
Any adverse drug experience, the specificity or severity of which is not consistent with the package insert for marketed products.

Relationship to Investigational Product
The assessment of the relationship of an adverse event to the administration of study drug (Remote/conditional, possible, probable, definite, none/doubtful) will be assessed as per the SOP No: APL-CPD-222-XX.

All clinically important abnormal laboratory results occurring during the study should be revaluated at adequate time intervals until they return to baseline values, to an acceptable level according to the clinical investigator or until a diagnosis that explains said changes is made.

The criteria to determine whether an abnormal test result should be reported as an adverse event are the following:

- When the test result is accompanied by an associated symptom
- When the test result requires an additional diagnostic examination or medical/surgical intervention.
- When the test result leads to a change in the study drug dose or study discontinuation, introduction of a significant concomitant drug treatment or other therapy.
- When the test results leads to any of the outcomes included in the definition of serious adverse event
- When the test result is considered by the Clinical Investigator as an adverse event.

11.0 BIOANALYTICAL PROCEDURE AND SAMPLE ANALYSIS

11.1 Sample Analysis

Samples from 24 subjects completing the cross-over will be assayed for plasma Amoxicillin using developed and validated LC-MS-MS method. Samples from subject withdrawn / dropped out will not be assayed, and will be replaced with standby subjects having the same sequence, as instructed by Principal Investigator, wherever possible. All samples from each subject will be analysed on the same standard curve. Quality control samples will be distributed through each batch of study samples assayed as per SOP No: APL-CPD-422-XX. The analysts will not have access to the randomization schedule (for drug dispensing).

11.2 Procedure for Re-analysis

Repeat analysis for both pharmacokinetic and analytical anomalies will be performed wherever required as per repeat analysis SOP No:APL-CPD-423-XX. Both initial and repeat analysis concentrations will be reported in the table form.

11.3 Recording and Reporting of Data on Drug Levels

Analytical results will be presented in tabular form in the bioanalytical report. Additionally, accuracy, precision and linearity data for each standard curve and all quality control samples will be presented.

12.0 DATA MANAGEMENT

12.1 Data Entry

Subject-wise, period-wise generated data of plasma Amoxicillin levels will be transferred electronically from bioanalytical Unit to Pharmacokinetic and Biostatistical Unit for pharmacokinetic and statistical analysis as per the SOP of the Bioanalytical Unit, CPD, Aurobindo Pharma Ltd.

12.2 Pharmacokinetic Parameters and Analysis

Pharmacokinetic parameters for plasma Amoxicillin will be evaluated with WinNonlin software version 3.3. Pharmacokinetic parameters for plasma Amoxicillin will be calculated as follows:

C_{max}	Maximum measured plasma concentration over the time span specified.
AUC_{0-t}	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method
$AUC_{0-\infty}$	The area under the plasma concentration versus time curve from time 0 to time infinity. $AUC_{0-\infty}$ is calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable plasma concentration (C_t) to the elimination rate constant $k_{el.}$ $AUC_{0-\infty} = AUC_{0-t} + C_t / k_{el.}$
AUC %Extrap	The % extrapolation calculated a $\frac{AUC_{0-\infty} - AUC_{0-t}}{AUC_{0-\infty}} * 100$
T_{max}	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

k_{el}	Apparent first order elimination rate constant calculated from a semi-log plot of plasma concentration versus time point. The parameter will be calculated by linear square regression analysis using the last 3 (or more) non-zero plasma concentrations.
$T_{1/2}$	The elimination or terminal half-life will be calculated as 0.693 /k_{el}.

If predose concentration is less than or equal to 5% of C_{max} value in any subject, that subject data will be included in all pharmacokinetic calculations without any adjustments. If the predose value is greater than 5% of C_{max}, that subject will be dropped for pharmacokinetic calculations.

12.3 Statistical Analysis

Statistical analyses will be performed on pharmacokinetic parameters using the SAS software version 8.2. The analyses will include data from subjects 1 to 24, if all these subjects complete the study. In case of drop-outs, samples of the alternate subject having the same sequence of dosing as that of the dropout will be taken up for analysis. Subsequent dropouts will not be replaced. If necessary, an unequal number of subjects per sequence will be used. Data from the subjects who vomit during the course of the study will not be considered for statistical analysis if vomiting occurs at or below 2 times median T_{max}. If a pharmacokinetic parameter cannot be determined for one period, the corresponding subject will be excluded for that particular statistical comparison. The statistical analysis will be done with the repeat value(s) of the samples retested for pharmacokinetic reasons. A separate analysis will be performed with the original values.

12.3.1 Summary Statistics

Mean, standard deviation and coefficients of variation will be calculated for the Subjects demographic variables like age, height, weight and BMI, plasma concentrations of Amoxicillin at each time point as well as for the pharmacokinetic parameters of Amoxicillin (C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, k_{el} and $T_{½}$). In addition, following statistical information will be provided for AUC_{0-t}, $AUC_{0-\infty}$, C_{max} :

i) Geometric Mean
ii) Arithmetic Mean
iii) Ratios of Mean
iv) 90% Confidence Intervals

12.3.2 Analysis of Variance (ANOVA)

The Lntransformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) for Amoxicillin will be statistically analysed using General Linear Model (PROC GLM) of SAS® software. The factors included in this model will be the treatment received, the period at which it is given alongwith the sequence in which each treatment being received and the subject effect (nested with sequence effect will

be tested using the subject nested within sequence mean square from the ANOVA as the error term. Each analysis of variance will include calculation of least square mean (LSM). Two one-sided test at 5% level of significance will be used to compare the average values of pharmacokinetic parameters determined after administration of test and reference products.

12.3.3 Confidence Intervals and Ratio Analysis

90% confidence intervals for the exponential of the difference between the test and the reference product will be calculated for the Lntransformed pharmacokinetic parameters of Amoxicillin. To establish BE, the calculated 90% confidence interval for Amoxicillin should fall within a BE limit, 80-125% of the ratio of the product averages.

12.3.4 Intra Subject Variability

Intra subject variability for the Amoxicillin subject plasma data will be calculated and reported.

12.3.5 Interim Analysis

No interim analysis of the study data will be done.

12.3.6 Documentation

Entire data, except the analytical data, lab investigation reports and other tests generated during conduct of the study will be directly recorded in raw data forms as per the related SOPs of APL-CPD. Results of lab investigations and other tests will be transcribed into laboratory report format as per SOP No.APL-CPD-315-XX.

Clinical raw data consists of medical history, physical examination and clinical laboratory reports, adverse reaction documentation and actual clock times of dosing and sample collection. The bioanalytical raw data will consist of chromatograms of all subjects and the forms filled for recording the study related activities. The statistical raw data consists of WinNonlin and SAS output.

The computer-generated chromatograms will also be treated as bioanalytical raw data. Raw data will be completed by the study personnel and checked by the respective immediate supervisors wherever applicable. All clinical raw data related to the study will be in the custody of Clinical Investigator or his designate and analytical raw data in the custody of Bioanalytical investigator or his designate until archiving.

12.3.7 Accessibility

Accessibility of the raw data will be limited to the IRB, QAD and the regulatory agencies for scheduled inspection and audits

13.0 ETHICAL CONSIDERATIONS

13.1 Institutional Review Board

This study will be carried out as per the ICH, 'Guidance for Good Clinical Practices (GCP)' and the principles of Declaration of Helsinki. The IRB shall review the protocol and the informed consent form for this study and no study specific procedures will be carried out until a written approval is obtained from the IRB.

13.2 Informed Consent

Approval from IRB will be taken for informed consent documents (English and relevant translations) before initiation of the study. Informed consent documents will be made in a language understandable by volunteers. Informed consent will be obtained as per SOP No.APL-CPD-207-XX.

13.3 Volunteer Compensation

The subjects will be suitably compensated for their participation in the study, as per the SOP No. APL-CPD-230-XX, titled, 'Compensation for volunteers / subjects for clinical study'.

13.4 Protocol Amendments and Approval from IRB

Any change or addition to this protocol requires a written protocol amendment that must be approved by IRB before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, will also require approval by the IRB.

Examples of amendments requiring such approval are :

- An increase in drug dosage or duration of exposure of subjects
- A significant change in the study design
- An increase in the number or the amount of blood draw
- Addition or deletion of a test procedure for safety monitoring

These requirements for approval will in no way prevent any immediate action from being taken by the clinical investigator in the interests of preserving the safety of the subjects included in the study. If an immediate change to the protocol is felt necessary by the Clinical Investigator and is implemented for safety reasons, the IRB will be notified within 10 working days. Amendments affecting only administrative aspects of the study will not require formal protocol amendments or IRB approval but the IRB will be kept informed of such administrative changes.

13.5 Confidentiality of Data

The data identifying study subject's name will be kept confidential and will be accessible only to concerned study personnel, quality assurance department, and if necessary, IRB and regulatory agencies.

13.6 Publication Policy

Publication of the results of the study, whether in whole or in part, shall be within the sole and absolute discretion of Director, APL-Research Centre.

13.7 Study Deviations

Study will be conducted in accordance with the Protocol, SOPs (Standard Operating Procedures) and regulatory requirements. Deviations (if any), at any stage of the study will be recorded promptly and corrective action will be taken.

14.0 SUMMARY AND FINAL REPORTS

Clinical report, bioanalytical report (including chromatograms of 20% of subjects serially selected through randomization) and biostatistical report will be prepared giving details of each operation conducted. The summary report will also be prepared which will contain main points of the clinical, bioanalytical, biostatistical report and pharmacokinetic data, figures and tables of mean and individual subject plasma concentrations and pharmacokinetic profiles. Copies of the protocol, informed consent document, letter of approval from the IRB and randomization schedule will be appended to the summary report.

15.0 QUALITY ASSURANCE AUDITS

The actual conduct of the study during the various phases and the raw data generated during the course of the study will be liable for inspection and quality audit for conformance to this protocol and all the governing APL-CPD SOPs by Head-Quality Assurance department or his designate. An audit schedule will be drawn prior to the study. Audit reports will be issued. After corrective actions have been taken and reviewed, QA authentication statement will be issued, which is included in the study report.

16.0 ARCHIVES

A representative sample of the test and reference drug products used in the study will be archived. Electronic copies (if generated) or else the paper copies of the entire raw data (Including chromatograms, SAS, WinNonlin outputs, PK data, forms filled both in the clinical and bioanalytical sections, medical screening records, X-ray reports and clinical investigations reports) generated during the study alongwith a copy of the protocol, informed consent form and its amendments, audit reports, IRB correspondence will be archived in APL-CPD for a period of 15 years.

17.0 BIOWASTE DISPOSAL

All the biowaste generated during the clinical and analytical phases of the study will be managed as per the SOP No.APL-CPD-113-XX.

18.0 REFERENCES

18.1 Medical Economic Company Inc, Physician's Desk Reference, 57th Edition, 2003, P.1456-60.

18.2 Churchill Livingstone, Colin Dollery, Therapeutic Drugs, IInd edition, Volume I, 1999, P. A162-A165.

18.3 Pharmaceutical Press, Martindale-the complete drug reference, 33rd edition, P.149-150

18.4 http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentsID

19.0 LIST OF APPENDICES:

Protocol will have the following Appendices.

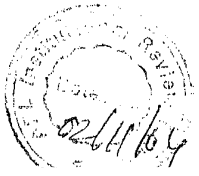
Appendix – 1 Study Flowchart

Appendix – 2 Event Schedule

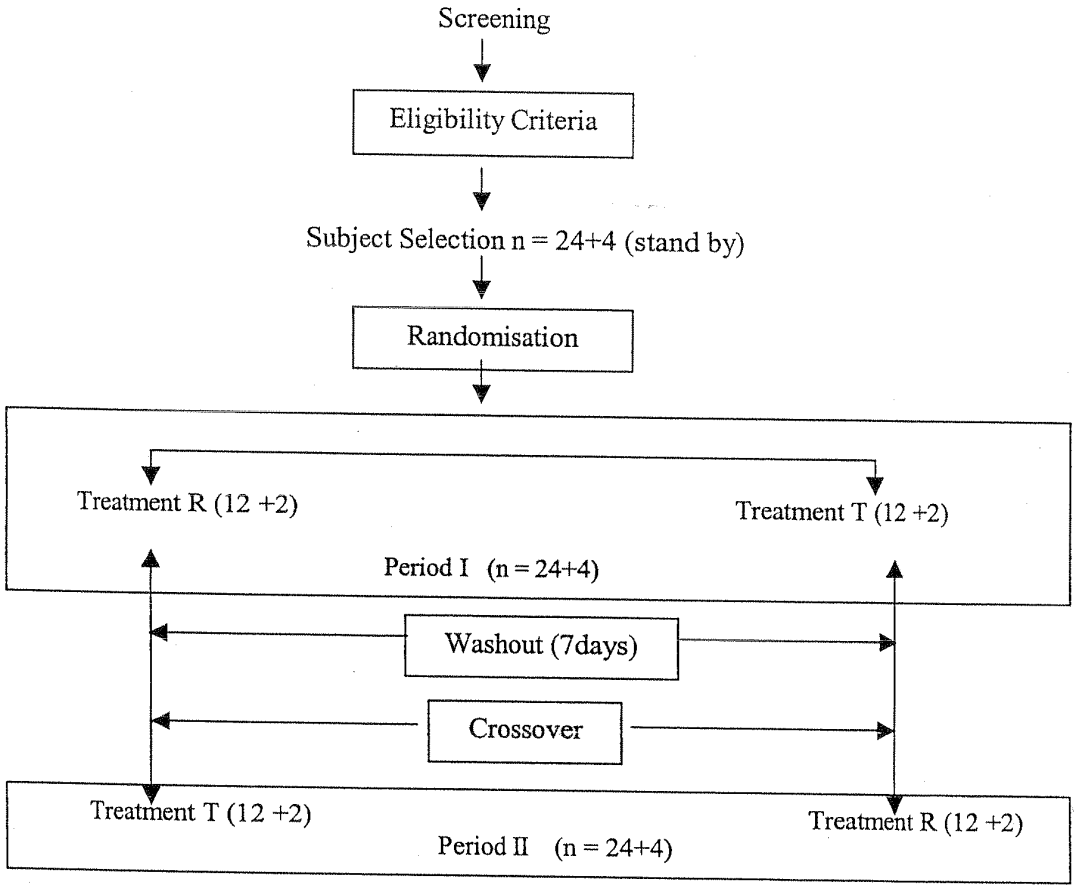
Appendix – 3 Blood Sampling Schedule

Appendix – 4 Investigator CVs

Appendix – 5 Declaration of Helsinki



APPENDIX – 1
STUDY FLOW CHART (CLINICAL)



n - Number of subjects
R - Reference Product
T - Test Product

APPENDIX – 2

EVENT SCHEDULE

Sl.No	Requirement		Screening	Period-I			Period-II		
				Check-in	Dosing Day	Check-out	Check-in	Dosing Day	Check-out
1	(*)Informed consent		•	•					
2	Demographics		•						
3	Medical history		•						
4	Medical examination	General and systemic examination	•						
		Vitals	•	•	•	•	•	•	•
		ECG (12 lead)	•						•
		Chest X-ray (PA view)	•						
		Post study examinations							•
5	Subject well being questionnaire				•			•	
6	Clinical laboratory tests	Hematology: RBC count, hemoglobin, Total & differential WBC count & platelets count	•						•
		Blood grouping & Rh typing and bleeding time	•						
		LFT: SGOT, SGPT, Total bilirubin , alkaline phosphatase, and γ – GT, total protein and albumin.	•						•
		Serum electrolytes: {serum sodium, potassium & chloride, calcium and phosphorous, Serum total cholesterol	•						
		Blood glucose (Fasting)	•						
		RFT: serum creatinine, serum urea and serum uric acid.	•						•
		(**) CUE	•						
		Drugs of abuse in urine: {benzodiazepine, opioids, amphetamine, cannabinoids & barbiturates}(***)	•	•			•		
		Screening for infectious diseases: {HIV 1 & 2, HBs(Ag), HCV and RPR}	•						

(*)Informed consent procedure would be obtained as per Sop no. APL-CPD- 207-XX.

(**) CUE (Complete Urine Examination), which includes physical, bio-chemical and microscopic examination.

(***)Screening for drugs of abuse in urine will be done only once if the volunteer is screened on check-in day of Period-I

Skin examination for maculopapular rash and absolute eosinophil count will also be done at the end of period-II at the time of checkout

APPENDIX- 3
BLOOD SAMPLING SCHEDULE

Sample No.	Sampling Time (hours)	Clock Time**
1	0.0(pre-dose)	7:15am
	Dosing	8:00 am
2	0.25	8:15 am
3	0.5	8:30 am
4	0.75	8:45 am
5	1.0	9:00 am
6	1.33	9:20 am
7	1.67	9:40 am
8	2.0	10:00 am
9	2.33	10:20 am
10	2.67	10:40 am
11	3.0	11:00 am
12	4.0	12:00 noon
13	5.0	1:00 pm
14	6.0	2:00 pm
15	7.0	3:00 pm
16	8.0	4:00 pm
17	12.0	8.00 pm

**Clock time may change according to exact time of administration of the drug.
0.25-12.0 hour samples are post dose samples

02/11/04

Appendix-4
CURRICULUM VITAE

Name: N.Nagaraj Kumar

EDUCATIONAL QUALIFICATIONS

Master of Pharmacy in Pharmacology, KLE College of Pharmacy, Belgaum, India, under Rajiv Gandhi Unversity of Health Sciences, Bangalore, India. (1996-1998).

PROFESSIONAL WORK EXPERIENCE

- Presently, Scientist, Clinical Pharmacology Department, APL Research Centre, Hyderabad, India (December 2002 to till date)
- Project Manager, Nicholas Piramal India Ltd-Well quest CRO, Mumbai, India (January 2001 to December 2002)
- Pharmacologist, Vimta Labs Ltd, Hyderabad, India (November 1998 to December 2000)

51/2 years research experience covering Bioavailability, Bioequivalance, studies.

Extensive exposure in overall study conduct/management of more than 100 Bioequivalance studies submitted to various regulatory agencies.

Experienced in developing and validating bioanalytical methods, pharmacokinetic analysis using WinNonlin software, preparation of study protocols/ICF documents, clinical, bioanalytical and summary reports, SOPS and management of IRB related activities.

Having major contributions in establishing/placing systems up to the standards at associated organizations.

Handling experience of various Clinical and Bio analytical equipments relevant to bio studies.

Organised/Attended several training sessions, workshops and seminars on GCP and GLP.

Signature:

Date: 18/06/04

APPENDIX – 4
CURRICULUM VITAE

NAME: Dr. Ashis Patnaik

EDUCATIONAL QUALIFICATIONS :

- MD (Pharmacology) from M K C G Medical College, (Berhampur University), Berhampur, ORISSA.
- MBBS, M K C G Medical College, (Berhampur University), Berhampur ORISSA.

PROFESSIONAL WORK EXPERIENCE :

- Presently working as Scientist –Clinical Pharmacology in Clinical Pharmacology Department of APL Research Center, Hyderabad from May 10, 2004 to till date.
- Worked as Asst. Professor in Pharmacology, J.N. Medical College, Sawangi (M), Wardha from 02.10.2002 to 03.05.2004.
- Worked as Class-II Medical Officer in Primary Health Centre, Kuldhia, Dist. Mayurbhanj, Orissa from July 1997 to July 1999.

Signature : **Date :** 28/08/04

Institutional Review Date

APPENDIX-4

CURRICULUM VITAE

NAME: DR. SAJJAD ANWARPASHA DESAI

EDUCATIONAL QUALIFICATIONS

- M.D.-Pharmacology from DR.V.M.Medical College, Solapur, Maharashtra (Shivaji University)
- M.B.B.S. from Government Medical College, Miraj, Maharashtra (Shivaji University)

PROFESSIONAL WORK EXPERIENCE

- Presently working as `Scientist-Clinical Pharmacology' in Clinical Pharmacology Department of APL Research Center, Hyderabad from October 2003 to till date.
- Worked as Manager-Clinical Research with Lupin Limited (Research Park), Pune from August 2002 to September 2003.
- Worked as Lecturer in the Department of Pharmacology Government Medical College, Miraj for a period of 6 months from February 2002 to August 2002.
- Worked as Assistant Lecturer in the Department of Pharmacology DR.V.M.Medical College, Solapur for a period of 22 months during August 1998 to February 2002.
- Worked as Class-II Medical Officer (rural service) at primary health center, Phonda, Dist-Sindhudurga, Maharashtra October 1997 to August 1998.

Signature: Desai Date: 27/08/04

APPENDIX-4

CURRICULUM VITAE

Name: Avinash B. Gaikwad

EDUCATIONAL QUALIFICATION:

Master Of Science in Analytical Chemistry, Nowrosjee Wadia College, Pune University, India (1995-1997).

PROFESSIONAL EXPERIENCE:

Bioanalytical Research and Development professional with 7 years in Pharma industry. Conducted more than 100 Bioequivalence studies as per FDA guidelines. A strong background in bioanalytical method development and its validation. Hands on sophisticated equipments like HPLC with UV, Fluorescence Detector, LC-MS, LC-MS/MS, Solid Phase Extraction techniques, UV-VIS Spectrophotometer. Well versed with recent trends in GLP.

WORK PROFILE:

March 04 – Present: Research Scientist II, APL Research Centre.
Jan 2003 – March 04: Sr. Research Associate, Wockhardt Research Centre, Aurangabad.
Jan 2000-Jan 2003: Reseacr Associate-II, Wockhardt Research Centre, Aurangabad.
Sep 1998- Jan 2000: Research Associate-I, Wockhardt Research Centre, Aurangabad.
Sep 1997- Sep 1998: Trainee Research Asssociate, Wockhardt Research Centre, Aurangabad.

AVINASH B. GAIKWAD

Date : 15/09/09

Appendix-4

CURRICULUM VITAE

NAME:P. PRAMOD KUMAR REDDY

EDUCATIONAL QUALIFICATION:

Msc.(STATISTICS),University College of Science, OsmaniaUniversity, Hyderabad.

PROFESSIONAL WORK EXPERIENCE:

- Working as a Research Associate at Pharmacokinetics & Biostatistical Unit, Clinical Pharmacology Department, APL Research Centre, Hyderabad from 3rd August, 2004.

Signature: Pramod

Date: 02/09/2004

02/09/04

APPENDIX-5

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

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26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. *(See footnote*)*

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

**FOOTNOTE:*

Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebocontrolled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method;

or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

♣ ♣ ♣

6.10.2002

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

Informed Consent Document

Title:

An open label, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Amoxicillin 500 mg capsules (Test) of Aurobindo Pharma Ltd., India and Amoxil (Reference) capsules of GlaxoSmithkline, UK, in 24 healthy, adult, male, human subjects under fasting conditions.

Volunteers Name: _____ _____ _____
(First Name) (Last Name) (Surname)

Date of Birth: _____(d d /mm /y y)

Age: _____ (completed years)

Address: _____

_____

_____

Telephone No.: _____

It is important to read carefully and understand the information given in this document before agreeing to participate in the current study. You must sign this document in duplicate and retain a copy of this document for future reference. All clarifications and questions must be discussed during the oral presentation of this document.

The purpose of this document is to clearly state the procedures of the study and to ensure that you enter the study only after knowing all relevant facts about it. The informed consent form describes the purpose of the study, possible benefits, risks or discomfort, alternative treatment and confidentiality. It also bears the declaration of your voluntary participation in the study.

The informed consent is not a contract and you can withdraw from the study at anytime, at your own will.

Volunteer Signature _____ Date _____

Signature of the Physician/Clinical Investigator ___ e _____

1. Introduction

Amoxicillin is an antibiotic belongs to the Penicillin class. This medicine is used to kill the bacteria or germs that cause infections. Therefore, this medicine is used to treat infections of the chest, ear, nose, throat, urinary systems, skin and gonorrhea.

2. Why is this study being done?

This study involves research. The aim of this study is to check that Amoxicillin capsules manufactured by Aurobindo Pharma Ltd., India are equivalent to that of the established marketed Amoxicillin in UK under the brand name of Amoxil.

3. What is the purpose of the research?

Amoxicillin is an antibiotic drug sold in UK under the brand name of Amoxil capsules. Aurobindo Pharma Ltd., India, has manufactured same strength of Amoxicillin capsules and would like to sell in UK. In order to achieve this Aurobindo Pharma has designed a research study in human beings to show that equivalent amount of Amoxicillin is present in blood when either capsules manufactured by Aurobindo Pharma or GlaxoSmithkline, UK are given to same human being at different time.

4. Description of the study

4.1. What are the Inclusion Criteria?

You will be `eligible' to participate in the study only when you satisfy all of the following criteria:

4.1.1. You are male with in age group of 18 to 50 years.

4.1.2. You have a body mass index between 19 and 26.

4.1.3. You are willing to provide written informed consent to participate in the study.

4.1.4. You have no disease markers for HIV 1&2, Hepatitis B&C virus and Syphilis.

4.1.5. You have no significant disease or no clinically significant abnormality in laboratory test results, medical history or physical examination during screening.

4.1.6. You have a normal 12 lead ECG.

4.1.7. You have a normal chest X-ray (PA view).

4.1.8. You are compliant with requirements of the entire protocol.

4.1.9. You have no history or evidence of allergy or hypersensitivity to Amoxicillin and other penicillins and Cephalosporins.

4.1.10. You have no history of significant systemic disease.

4.1.11. You have no history of psychiatric disorders.

Signature of Volunteer : _____ Date: _____

4.1.12. You have no history of addiction to any recreational drug or drug dependence.

4.1.13. You have not donated blood (one unit or 350 ml) within 56 days prior to receiving the first dose of study medication.

4.1.14. You have not participated in any clinical study within the past 56 days.

4.1.15. You have not received any prescription drugs (e.g.: probenecid and allopurinol) within the two weeks prior to receiving the first dose of study medication.

4.1.16. You have not received any over-the-counter (OTC) drugs like Cold preparations, and antacid preparations vitamins and natural products used for therapeutic benefits within two weeks prior to receiving the first dose of study medication.

4.1.17. You have no history of dehydration from diarrhoea, vomiting or any other reason within a period of 24 hours prior to the study.

4.1.18. You have no family history of neurological disorders.

4.1.19. You should not take any medication until last blood sampling time point of period-II without investigator's consent.

4.1.20. You have negative results for drugs of abuse (Barbiturates, Benzodiazepines, Opioids, Amphetamine and Cannabinoids) in urine during pre-study screening and during the day of check-in for Period-I & II.

4.1.21. No history of malaria and absence of psoriasis.

4.2 What are the Exclusion Criteria?

You will be 'ineligible' to participate in this study if you satisfy any one of the following criteria

4.2.1 If you have history of convulsions.

4.2.2 If you have history of regular alcohol intake for more than 2 units per day in any form either beer/ wine/ whisky/ country liquor/ brandy/ gin/ rum or if you use alcohol within 48 hours before the study or if you have difficulty in abstaining from alcohol for the duration of study.

1 unit of alcohol = 30ml of spirit or 1 pint of beer.

4.2.3 If you consume more than 5 cups of coffee or tea/day or tobacco (more than 9 cigarettes/ beedies/ cigars/day).

4.2.4 If you have history of difficulty with donating blood or if you have difficulty in accessibility of veins in left or right arm.

4.2.5 If you have received any prescription drugs (eg: probenecid and allopurinol) within the two weeks prior to receiving the first dose of study medication.

4.2.6 If you have received any over-the-counter (OTC) drugs (e.g.: Cold preparations, and antacid preparations vitamins and natural products used for therapeutic benefits), within two weeks prior to receiving the first dose of study medication.

4.2.7 If you have taken an unusual (or) abnormal diet for whatever reason e.g. because of fasting due to religious reasons.

4.3. Study Procedure

4.3.1 You will be required to undergo various screening tests which include medical examination, blood tests, urine tests, tests for infectious diseases (HIV 1 & 2, hepatitis B & C virus and RPR), Chest X-ray (PA view) and 12-lead ECG at the time of screening. Approx. 9 mL blood will be taken for screening. You have to give approximately 20-25 mL urine sample for urine tests.

4.3.2 At the end of the period-II, 7 ml blood will be taken at the time of 12.0 hour blood sample for the blood tests (Hematological Investigations including absolute eosinophil count, RFT, LFT). 12-lead ECG and skin examinations for maculopapular rash will also be done at the time of 12.0 hour blood sample collection of period-II.

4.3.3 In case if you are withdrawn/dropped out from study by any reason (before completion of the study and after the dosing in period-I) safety assessments mentioned in section: 4.3.2 will also be done.

4.3.4 You will be eligible for admission into the study only after you satisfy all the laboratory tests, medical examination, and study protocol requirements.

4.3.5 Study will be in two periods. In each of the two periods you will be required to check-in at APL-CPD center atleast 10.0 hours 45 minutes before the administration of any drug dose i.e. the previous evening to Day –1 (day of drug administration).

4.3.6 Eligibility criteria, which include vitals, will be done at the time of check-in, in each period.

4.3.7 You will be required to stay at Clinical Unit, CPD, APL Research Center, Mirra Multispeciality Hospital, Plot Nos. 33-35, Alluri Sitaramaraju Colony, Opp. J.P.N.Nagar Colony, Miyapur, Hyderabad-875 050 for two periods i.e. Period-I and Period- II.

4.3.8 In Period-I you will receive either Reference R (Amoxil 500 mg capsule manufactured by GlaxoSmithkline, UK) or Test T (Amoxicillin 500 mg capsule manufactured by Aurobindo Pharma Ltd., India). The order in which you receive study medication will be decided randomly by us and will not be known to you.

4.3.9 There will be a wash out period of atleast 7 days between two periods.

4.3.10 Urine tests for drugs of abuse (Barbiturates, Benzodiazepines, Amphetamines, Opioids and Cannabinoids) will be conducted during the pre-study screening and on the day of check-in for period I and II, for which you have to give approx. 20-25 mL of urine sample in both the periods. However screening for drugs of abuse in urine will be done only once, if you are screened on the day of check-in for Period-I.

4.3.11 In Period-II you will receive the alternate medication (if you have received Reference R in Period-I, you will receive Test T in Period-II).

4.3.12 In each period, after an overnight fast of atleast 10 hours you will receive, orally, a single capsule of Amoxicillin (500 mg) with 240 mL of water.

4.3.13 Your drug dosing will be in sitting posture and you will be instructed to remain seated or ambulatory for the first 2.0 hours following drug administration. Thereafter you will be allowed to engage only in normal activities while avoiding severe physical exertion. A post dose standardized meal consisting of approx. 1300 Kcal as per the meal plan provided by the dietician will be provided at 4.0 hours 15 minutes (lunch consisting of approx. 900 Kcal) and 8 hours 30 minutes (snacks consisting of approx. 400 Kcal) respectively, whereas the dinner (consisting of approx. 1000 Kcal) will be provided during the day of check-in.

4.3.14 In case the mealtime coincides with the sample collection time, vitals and subject well being questionnaire, the sequence of events would be followed as: Blood sampling, vitals, subject well being questionnaire and meals.

4.3.15 Blood samples will be collected during each period. Blood samples will be collected through an indwelling cannula (small plastic tube) placed in a forearm vein. First blood sample (pre-dose) will be collected before Amoxicillin dose administration.

4.3.16 After Amoxicillin administration (post-dose) blood samples will be collected at 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 12.0 hours post dose.

4.3.17 At every time point 6 mL of blood will be collected.

4.3.18 Intravenous indwelling cannula would be kept in place as long as required by injecting 1 mL of 5 IU/mL of heparin (a substance normally present in human body) in normal saline solution to prevent blood clotting and facilitate blood sample collection.

4.3.19 At the discretion of the attending Physician or Clinical Investigator blood may also be withdrawn by a fresh clean veinpuncture using a disposable sterilised needle and vacutainer whenever cannula is blocked.

4.3.20 Combining two periods, the total number of blood samples collected will be 34 (17x2), the total volume of blood withdrawn will be 254 mL. (Approx. 9 mL for

screening and 34 mL discarded blood prior to collection through the venous cannula, 204 mL for both the periods and 7 mL for post-study lab investigations (at the end of Period-II) unless otherwise you are withdrawn or dropped out from the study by any reason.

4.3.21 You are advised to abstain from alcohol, cigarettes, tobacco products and any form of xanthine (chocolates, tea, coffee or cola drinks) containing food and beverages atleast 48 hours prior to drug dosing in each period and during your in-house stay.

4.3.22 All drug and/or study related adverse events would be treated by the attending physician either at Clinical Unit, CPD or Mirra Multispeciality Hospital or tertiary Hospital at no cost to you.

4.3.23 You will be discharged at the end of 12.0 hour post dose, sample collection of the study, if you are in good health and not suffering from any adverse events. In case of any adverse events, you will be given proper medical care and kept under observation until recovery.

4.3.24 Your approximate duration of stay at Clinical Unit, CPD would be approximately 30 hours for each period.

4.3.25 You will be informed in the event of new information that may be relevant to take decision regarding your participation in the study.

4.3.26 Twenty-four subjects will be involved in the study and 4 (four) subjects are standby subjects.

5. What are the risks of the study?

Amoxicillin is already marketed in many countries and in India for the last few years. Generally, it is well-tolerated drug. However, side effects are known to occur in few people. These side effects are reported to occur on long terms use of drug.

We anticipate that there will be no serious side effects if one capsule is administered to the healthy human subject. This is only our assessment but mild side effects can occur.

Nausea (a discomfort feeling of vomiting), vomiting, diarrhea (loose stools) and hemorrhagic/ pseudomembranous colitis.
Various skin reactions
Moderate rise in Liver function tests, swelling in liver and Jaundice (yellow skin)
Changes in hemoglobin content and reduction in various types of white blood cells
Discoloration of the tooth (rare).
Agitation, anxiety, insomnia (unable to get sleep), confusion, convulsions (fits), behavioral changes, and/or dizziness have been reported rarely.
The procedure of taking blood may cause local discomfort, bruising, swelling and rarely a local infection, at the site of cannula insertion and dizziness.

6. **Are there benefits for taking part in the study?**

You will not have any direct benefits from the study. Since you do not require treatment with any of the study drug medications, you are unlikely to be benefited by taking these medications. By participating in this study you will get a free medical check-up, a study participation fee (compensation for volunteers), plus your probable satisfaction of serving the interest of drug research.

7. **What other options are there?**

This study is for research purpose and the only alternative for you would be not to participate.

8. **What about confidentiality?**

Your medical records obtained during the study will be maintained in confidentiality.

The following organisations may monitor this study/related records and data for quality assurance and data analysis:

- Concerned regulatory authority (like ANVISA Brazil, US-FDA / UK-MHRA, DCG(I)).
- Designated personnel / Investigator: QAD/CPD of APL RC.
- Members of APL Institutional Review Board

Accessible reports will however not disclose any information that reveals the identity of any specific volunteer.

9. **What is the financial compensation?**

You will not be paid for any loss of wages for the days of your participation into the study. To compensate you for your discomfort and inconvenience, a total compensation of Rs.2, 175/- will be paid. In case of premature withdrawal from the study you will be entitled to the following compensation.

Reasons of withdrawal from the study	Compensation
You are dropped from the study on medical decision, for your health interest by the Clinical Investigator/attending Physician.	Full payment
After initiation of the study you withdraw on your own free will	100% proportionate participation dues as per SOP No. APL-CPD-230-XX.
You are withdrawn from the study on compassionate grounds, with the permission of the Clinical Investigator/attending Physician	100% proportionate participation dues.
You are dropped from the study by the Clinical Investigator/ attending Physician after signing the Informed Consent Form but before receiving any medications due to your violation of requirements of the study	No payment
You are dropped from the study by the Clinical Investigator/ attending Physician because of violating Do's and Don'ts of Clinical Unit, CPD/ Indiscipline.	No payment
You are dropped/withdrawn by any other reason by Clinical Investigator/ attending Physician.	As decided by IRB

XX- Current Version Number of SOP

10. What will be the compensation for Adverse Events?

You will be treated completely either at Clincal Unit, CPD, or Mirra Multispeciality Hospital or any other tertiary Hospital for any Adverse Events encountered during your stay at clinical unit, CPD with out any cost to you. In case of any serious mishap, no fault compensation as decided by APL-IRB or as per the insurance policy, will be paid.

Signature of Volunteer : _____ Date: _____

11. What are my rights as I participate?

Your rights as a research volunteer and your safety will be protected by the APL Institutional Review Board, and APL-CPD will also assure the integrity, safety, rights and confidentiality of the study volunteers. Your participation in this study is voluntary. Your refusal to participate will involve no penalty. If you decide to voluntarily withdraw from this study, the Clinical Invesigator will promptly discuss with you the best means of orderly termination from this study. We assure you that your relations with APL-CPD or its staff will not be affected even if you prematurely withdraw from the study at your own free will with / without stating any reason.

12. What is expected from me?

You are requested to co-operate with the Clinical Unit, CPD staff. On arrival you and your baggage will be searched. Your personal belongings will be checked at the time of check-in during each period of the study. During your participation in this study you are expected to abide by the rules of the Clinical Unit, CPD and maintain discipline during the course of stay for the study.

13. What are the circumstances under which your participation will be terminated without your consent by the investigator?

13.1 Allergic reaction to the administered medicine.
13.2 Adverse events.
13.3 Non co-operative and does not follow the protocol.
13.4 If you vomit soon after the drug administration (As decided by the clinical investigator)
13.5 If you miss last 3 or last sampling time points.

14. What is the additional cost that may result to you if you participate?

You will be not required to pay any additional cost to APL (CPD) for your participation. All your conveyance, boarding and lodging will be looked after by APL-CPD. In addition, compensation as per SPO No. APL-CPD-230-XX will be given to you.

Signature of Volunteer : _____ Date: _____

15. Whom do I call if I have question or problem?

During the entire study period, you are free to obtain further information on any issue or subject. In case of any urgent questions related to the study needs advice, you may contact the following personnel at APL (CPD).

- Mr. N. Nagaraja Kumar, Mobile No. 94401-43138
- Dr.Nitn Kulkarni, Mobile No. 9440053449

Address:
Clinical Unit
APL-CPD
Mirra Multispeciality Hospital
2nd and 3rd Floor
Plot no: 33,34,35, Alluri Sitaramaraju Colony
Opp.J.P.N.Nagar Colony, Miyapur
Hyderabad-500 050
Tel: 91-40-23045809 / 91-40-23045709

If you have questions regarding your rights as human volunteer, you are free to call the Chairman of APL IRB:

Justice Y.V. Narayana (Retd.)
Chairman (APL- IRB)

Address: Flat No: 402 Pooja's Pride
Plot No: 75, Srinagar Colony
Hyderabad-500 073
Tel: 91-40-23743173.

Signature of Volunteer : _____ Date: _____

పాల్గొను వ్యక్తి గుర్తింపు నెం ..... ఫైనల్

ఈ పత్రాన్ని గురించి మౌఖికంగా చెబుతున్నప్పుడే మీ సందేహాలను, ప్రశ్నలను చర్చించి సమాధానం పొందాలి.

ఈ అధ్యయనానికి సంబంధించిన అన్ని వాస్తవాలను తెలుసుకున్న తరువాతే అధ్యయనంలో చేరేందుకు వీలుగా ఈ పత్రంలో అధ్యయన విధానాలను స్పష్టంగా తెలియచేయడం జరిగింది. ఈ అధ్యయనం ఉద్దేశ్యాన్ని, రాగల ప్రయోజనాలను, ప్రమాదాలను లేదా అసౌకర్యాలను, ప్రత్యామ్నాయ చికిత్సను, సమాచారాన్ని రహస్యంగా ఉంచడాన్ని గురించి వివేచనా పూర్వక అంగీకార పత్రం వివరిస్తుంది. ఈ అధ్యయనంలో మీరు ఇష్టపూర్వకంగా పాల్గొంటున్నట్లుగా చెప్పే ప్రకటన పత్రం కూడా ఉంది.

వివేచనా పూర్వక అంగీకారం కాంట్రాక్టు కాదు. మీరు ఏ సమయంలోనైనా దీనిలో పాల్గొనకుండా మీ ఇష్టప్రకారం వెళ్ళిపోవచ్చు.

క్లినికల్ పరిశోధకుని / వైద్యుని సంతకం..... తేది.....

వాలెంటీర్ సంతకము..... తేది.....

పాల్గొను వ్యక్తి గుర్తింపు నెం ..... ఫైనల్

1. పరిచయం:

ఏమోక్సిసిలిన్ అనే మందు పెన్సిలిన్ వర్గానికి చెందిన యాంటిబయాటిక్. ఈ మందును మానవ శరీరంలో వ్యాధికి కారణమైన బాక్టీరియా మరియు ఇతరక్రిములను చంపుటకు ఉపయోగిస్తారు. పైన చెప్పిన విధంగా ఈమందును ఛాతి, చెవి, ముక్కు, గొంతు, చర్మము, మూత్ర సంబంధమైన వ్యాధులను మరియు గనేరియాను తగ్గించే ందుకు ఉపయోగిస్తారు.

2. ఈ అధ్యయనాన్ని ఎందుకు చేస్తున్నాం?

పరిశోధన కోసం ఈ అధ్యయనం చేస్తున్నాం. ఈ అధ్యయనం యొక్క ముఖ్యలక్ష్యం ఏమిటంటే, అరబిందో ఫార్మా లిమిటెడ్, ఇండియా తయారుచేసిన ఏమోక్సిసిలిన్ మందు మరియు ప్రస్తుతం UK మార్కెట్ లో ఏమోక్సిల్ అనే బ్రాండ్ పేరుతో లభ్యమగుచున్న ఏమోక్సిసిలిన్ మందుకు సమానమగునని పరీక్షించి చూడటం.

3. ఈ పరిశోధన ఉద్దేశ్యమేమిటి?

ఏమోక్సిసిలిన్ కాప్సుల్ను శరీరంలో బాక్టీరియల్ వ్యాధిని తగ్గించేందుకు ఉపయోగిస్తారు. ఈ కాప్సుల్ UK మార్కెట్లో ఏమోక్సిల్ అనే బ్రాండు పేరుతో అమ్మబడుతూ ఉంది. అరబిందో ఫార్మా లిమిటెడ్ కూడా ఏమోక్సిల్ అంత సమానమైన మందును UK మార్కెట్లో ప్రవేశపెట్టుటకు తయారుచేసినది. అధ్యయనంలో భాగంగా అరబిందో ఫార్మా లిమిటెడ్ ఒక ప్రయోగాన్ని మానవుల్లో చేయుటకు రంగంసిద్ధం చేసింది. ఈ ప్రయోగంలో అరబిందో ఫార్మా లిమిటెడ్ తయారుచేసిన ఏమోక్సిసిలిన్ మరియు గ్లాక్సోస్మిత్క్లైన్, UK తయారు చేసిన ఏమోక్సిల్ అనే మందు ఒకే మానవునికి వేరువేరు కాలంలో నిరాహార పరిస్థితులలో ఇచ్చిన యెడల వాటి శాతం రక్తంలో సమానమేనని చూస్తారు.

4. అధ్యయనం గూర్చి వివరము :

4.1 ఈ అధ్యయనంలో పాల్గొనటానికి కావలసిన అర్హతలు:
క్రింద సూచించిన లక్షణాలు అన్నీ మీకు ఉంటే మీరు అధ్యయనంలో పాల్గొనటానికి అర్హులు.

4.1.1 మీరు 18 నుంచి 50 ఏళ్ళ మధ్య గల మగవారై ఉండాలి.

4.1.2 మీ శరీర బరువు సూచిక 19-26 మధ్యలోనే ఉండవలెను.

4.1.3 ఈ అధ్యయనంలో పాల్గొనటానికి లిఖిత పూర్వకంగా అంగీకారాన్ని తెలపటానికి సంసిద్ధంగా ఉండాలి.

4.1.4 మీకు హెచ్.ఐ.పి 1మరియు 2, హెపటైటిస్ బి, సి హైపర్ మరియు సిఫిలిస్ వ్యాధి లక్షణాలు ఉండరాదు.

4.1.5 పరీక్ష (స్క్రీనింగ్) చేసినపుడు మీ వైద్య చరిత్రలో, శారీరక పరీక్షల్లో, లాబొరేటరీ పరీక్షల్లో పేర్కొనదగిన వ్యాధులున్నట్లు ఫలితాలు రాకూడదు.

4.1.6 మీకు 12 లీడ్ ఇ.సి.జి సాధారణంగానే ఉండాలి.

4.1.7 మీకు ఛాతీ ఎక్స్ రే (పి ఏ దృశ్యము) సాధారణంగానే ఉండాలి.

4.1.8 ఈ ఒడంబడిక పత్రంలో పేర్కొన్న అవసరాలకు అనుగుణంగా (లక్షణాలన్నీ మీకు) ఉండాలి.

4.1.9 ఏమోక్సిసిలిన్‌కు, సెఫలోస్పోరిన్ మరియు ఇతర పెన్సిలిన్ మందులకు అతి సున్నితంగా స్పందించే గుణం మీకు ఉండరాదు.

4.1.10 మీకు శరీర అంతర భాగాలకు సంబంధించిన వ్యాధులు ఉండరాదు.

4.1.11 ప్రధానంగా పేర్కొనదగిన మానసిక రుగ్మతలు ఉండరాదు.

4.1.12 ఉత్తేజితం చేసే మత్తు మందులకు, మాదక ద్రవ్యాలకు మీరు బానిసలు కారు.

4.1.13 ఈ అధ్యయనంలో మొదటి మోతాదు మందును తీసుకొనే 56 రోజులలోపు మీరు రక్తదానం (ఒక యూనిట్ 350 మి.లీ.) చెయ్యరాదు.

4.1.14 గత 56 రోజులలోపు ఏ రోగ చికిత్సాధ్యయనంలో మీరు పాల్గొని ఉండరాదు.

4.1.15 అధ్యయనంలో మొదటి మోతాదు మందును తీసికొనే రెండు వారాలలోపు మీరు డాక్టరు రాసిన (ఉదాహరణకు: ప్రొబెనిసిడ్ మరియు అల్లోపూరినాల్) ఏ మందూ వాడరాదు.

4.1.16 డాక్టరు రాసివ్వని మందులను {ఉదాహరణకు: జలుబు మరియు కడుపు నందు మంటను తగ్గించేందుకు ఉపయోగించేవి, వైటమిన్స్ మరియు అయుర్వేదిక్ మందులు (జబ్బును తగ్గించెందుకు వాడబడునవి)} అధ్యయనంలో మొదటి మోతాదు మందును తీసుకొనే రెండు వారాలలోపు మీరు వేసుకొని ఉండరాదు.

4.1.17 ఏ కారణం చేతగాని అధ్యయనానికి 24 గంటలు ముందు అతిసారవ్యాధి వల్ల నిర్జలీకరణ, వాంతులు ఉండరాదు.

4.1.18 మీ కుటుంబంలో ఎవరికీ నరాలకు సంబంధించిన వ్యాధులు ఇంతకు మునుపు లేనిపై ఉండాలి.

4.1.19 మీరు అధ్యయనంలో చివరి రక్తం శాంపుల్ ఇచ్చేంతలోపు ఏకారణం చేత అయిన కాని ఏ మందునైనా తీసుకొనవలెనంటే పరిశోధకుని అనుమతితోనే తీసుకొనవలెను.

4.1.20 మీకు స్క్రీనింగు, పీరియడ్ 1 మరియు పీరియడ్ 2 కొరకు క్లినికల్ యూనిట్‌కు వచ్చినపుడు, మూత్రములో కొన్ని రకాల అబ్యూజ్ డ్రగ్సును కనుగొనుటకు నిర్వహించు లాబోరేటరి పరీక్షలలో మీరు అటువంటి డ్రగ్సు తీసుకోలేదని నిర్ధారణ అయి ఉండవలెను.

4.1.21 మీరు మలేరియా లేదా సొరియాసిస్ వ్యాధులకు లోనై ఉండరాదు.

4.2 ఈ అధ్యయనంలో మీరు పాల్గొనటానికి వీలుకాని అంశాలు:
క్రింద పేర్కొన్న లక్షణాలలో ఒక్కటి ఉన్నా అధ్యయనంలో పాల్గొనటానికి మీరు అనర్హులు:

4.2.1 మీకు పేర్కొనదగిన ప్రధాన తీవ్ర వ్యాధి ఉంది.

4.2.2 మీరు రోజుకు 2 యూనిట్ల కన్నా ఎక్కువ మద్యం (బీర్, వైన్, విస్కీ, దేశీయ మధ్యము, బ్రాందీ, జిన్ మరియు రమ్) తాగుతున్నా, లేదా అధ్యయనానికి 48 గంటలు లోపు మద్యం తాగినా, అధ్యయనం జరుగుతున్నపుడు మద్యం తాగకుండా ఉండలేకపోయినా మీరు అనర్హులు.
ఒక యునిట్ మద్యం = 30 మి.లీ. స్పిరిట్ లేదా 1 పింట్ బీర్.

4.2.3 రోజుకు అయిదు కప్పులకు మించి కాఫీ, టీ తాగినా లేదా తొమ్మిదికి మించి బీడీలు / చుట్టలు / సిగిరేట్లు తాగినా అనర్హులు.

4.2.4 రక్తదానం చేయటానికి పనికిరాకపోయినా, ఎడమ, కుడి చేతులలో నరాలు (రక్తనాళాలు) దొరకక పోయినా అనర్హులు.

4.2.5 అధ్యయనంలో మొదటి మోతాదు మందును తీసికొనే రెండు వారాలలోపు మీరు డాక్టరు రాసిన (ఉదాహరణకు: ప్రొబెనిసిడ్ మరియు అల్లోపురినాల్) ఏ మందూ వాడరాదు.

4.2.6 డాక్టరు రాసివ్వని మందులను {ఉదాహరణకు: జలుబు మరియు కడుపు నందు మంటను తగ్గించేందుకు ఉపయోగించేపి, వైటమిన్స్ మరియు అయుర్వేదిక్ మందులు (జబ్బును తగ్గించెందుకు వాడబడునపి)} అధ్యయనంలో మొదటి మోతాదు మందును తీసుకొనే రెండు వారాలలోపు మీరు వేసుకొని ఉండరాదు.

4.2.7 ఏ కారణం చేతనైనా, అలవాటులేని మరియు అసాధారణమైన ఆహారం తీసుకున్నా అనర్హులు. ఉదా: మత పరమైన కారణాల వలన మీరు ఎక్కువ కాలం ఉపవాసం ఉన్నచో అనర్హులు.

4.3 అధ్యయనం నిర్వహించే విధానం:

4.3.1 మీకు వివిధ ప్రాథమిక పరీక్షలు అంటే డాక్టరుచే పరీక్షలు, అంటే రక్తపరీక్షలు, మూత్రపరీక్షలు, అంటువ్యాధులకు సంబంధించిన పరీక్షలు (హెచ్ఐవి1&2, హెపటైటిస్ B&C మరియు ఆర్.పి.ఆర్), ఛాతీ ఎక్స్ రే (పిఎ దృశ్యము), 12 లీడ్ ఇసిజి స్క్రీనింగ్ సమయంలో ఉంటాయి. ప్రాథమిక పరీక్షలు కొరకు 9మి.లీ. రక్తం మరియు మూత్ర పరీక్షల కొరకు సుమారు 20-25 మి.లీ. మూత్రం ఇవ్వవలసి ఉంటుంది.

4.3.2 పీరియడ్ 2 లో చివరి రక్తనమూనా (12.0 గంటలు) తీసుకొన్న తరువాత, 7 మి.లీ. రక్తం, రక్తపరీక్షల {హెమటలాజికల్ ఇన్వెస్టిగేషన్స్ సంపూర్ణ ఇసినోఫిల్ పరీక్ష, ఆర్.ఎఫ్.టి మరియు ఎల్.ఎఫ్.టి} కొరకు ఇవ్వవలసి యుండును. 12 లీడ్ ఇ.సి.జి మరియు చర్మ సంబంద పరీక్షలు చేయబడును.

4.3.3 మీరు ఏ కారణం చేతనైనగాని పీరియడ్ 1 లో మాత్ర తీసుకున్న తర్వాత నుంచి అధ్యయనం పూర్తి అవ్వటానికి ముందుగా, అధ్యయనం నుంచి తీసివేయబడినచో లేదా తొలగినచో మీకు సెక్షన్ 4.3.2 లో చెప్పబడిన పరీక్షలు ఉంటాయి.

4.3.4 లాబోరేటరీ పరీక్షలు, వైద్య పరీక్షలు, ఈ అధ్యయనం ఒడంబడిక పత్రంలోని అన్ని ఆవశ్యకతలు సంతృప్తికరంగా ఉంటేనే మీరు అధ్యయనంలో పాల్గొనడానికి అర్హులు.

4.3.5 అధ్యయనం రెండుసార్లు జరుగుతుంది. మీరు ఈ రెండుసార్లు మందు మోతాదు తీసుకుంటానికి 10గంటల 45 నిమిషాలు ముందుగా అంటే మందు మోతాదు తీసుకొనే ముందురోజు సాయంత్రం క్లినికల్ యూనిట్, సిపిడి, ఎపిఎల్ పరిశోధనా కేంద్రానికి రావలసి ఉంటుంది.

4.3.6 ప్రతిపీరియడ్‌లోనూ క్లినికల్ యూనిట్, సిపిడి, ఎపిఎల్ పరిశోధనా కేంద్రానికి వచ్చినపుడు వైద్యపరీక్ష మరియు అర్హత కొరకు నిర్ణయించు ప్రమాణము ఉంటుంది.

4.3.7 మీరు మొదటిసారి (పీరియడ్1) మరియు రెండోసారి (పీరియడ్2) కూడా క్లినికల్ యూనిట్, ఎపిఎల్-సిపిడి కేంద్రం మీరా మల్టీస్పెషాలిటీ హాస్పిటల్, ప్లాట్ నెం.33-35, అల్వారి సీతారామరాజు కాలనీ, జె.పి.ఎన్ నగర్ కాలనీ ఎదురుగా, మియాపూర్, హైదరాబాద్-500 050 లో ఉండవలసి ఉంటుంది.

4.3.8 మొదటిసారి రిఫరెన్స్ R (ఎమోక్సిల్ 500 మి.గ్రా., కాప్సుల్ గ్లాక్సోస్మిత్‌క్లైన్, UK వారు తయారు చేసినది) లేదా టెస్ట్ T (అరబిందోఫార్మా లిమిటెడ్ తయారు చేసిన ఏమోక్సిసిలిన్ 500 మి.గ్రా. కాప్సుల్) గాని ఇస్తారు. అధ్యయనంలో మందును ఇచ్చేక్రమాన్ని యాదృచ్ఛికంగా నిర్ణయిస్తారు.

4.3.9 మొదటిమోతాదు తీసుకున్న తరువాత 7 రోజులు పూర్తయిన పిమ్మట రెండోమోతాదు ఇవ్వటం జరుగుతుంది.

4.3.10 పీరియడ్ 1 మరియు పీరియడ్ 2 కొరకు క్లినికల్ యూనిట్‌కు వచ్చినపుడు, మూత్రము లో కొన్ని రకాల అబ్యూజ్ డ్రగ్స్‌ను కనుగొనుటకు నిర్వహించు లాబోరేటరి పరీక్షల (బెంజొడియజెపిన్స్, బర్బిట్యురేట్స్, అంఫెటమైన్, ఒపియొఇడ్స్ మరియు కన్నబినొఇడ్స్) కోసం సుమారు 20-25 మి.లీ. మూత్రం ఇవ్వవలసి ఉంటుంది. అయితే మీకు స్క్రీనింగ్, పీరియడ్ 1 మొదటి రోజున చేసినచో, మీకు ఆరోజు ఒకే ఒకసారి మూత్రములో కొన్ని రకాల అబ్యూజ్డ్ డ్రగ్ పరీక్షలు నిర్వహించెదరు.

4.3.11 రెండోసారి మొదటిసారి తీసుకోని మందును ఇవ్వడం జరుగుతుంది. (అంటే మొదటిసారి రిఫరెన్స్ R ను ఇస్తే రెండోసారి టెస్ట్ T ని ఇస్తారు).

4.3.12 ప్రతిసారి సుమారు పది గంటలపాటు నిరాహారంగా ఉన్న తరువాత, ఏమోక్సిసిలిన్ 500 మి.గ్రా. కాప్సుల్‌ను 240 మి.లీ. నీటితో నోటిద్వారా తీసుకోవాలి.

4.3.13 మీరు కూర్చొని మాత్రను వేసుకోవాలి. మాత్ర వేసుకున్నాక రెండు గంటలపాటు కూర్చొని ఉండాలి. తరువాత శారీరకంగా శ్రమపడని కార్యక్రమాల్లో పాల్గొనవచ్చు. ప్రతిపీరియడ్‌లోనూ మాత్రను వేసుకున్న నాలుగు గంటల తరువాత ఆహార నిపుణుడు సూచించిన విధంగా మొదటిరోజు (మాత్రతీసుకున్న రోజు) సుమారు 1300 కి.కేలరీల ఆహారాన్ని క్రింద చెప్పబడిన విధంగా ఇస్తారు. మాత్ర వేసుకున్న నాలుగు గంటల పదిహేను నిమిషాలకు మధ్యాహ్నభోజనము (సుమారు 900 కి.కేలరీలు) మరియు ఎనిమిది గంటల ముప్పై నిమిషాలకు స్నాక్స్ (సుమారు

400 కి.కేలరీలు) ఇవ్వబడుతుంది. మాత్రతీసుకునే ముందురోజు రాత్రి డిన్నర్ (సుమారు 1000 కి.కేలరీలు) ఇవ్వబడుతుంది.

4.3.14 భోజన సమయం, పరీక్ష సమయం (అంటే వైటల్స్ మరియు సబ్జక్ట్ యొక్క క్షేమము ఉద్దేశించి అడిగే ప్రశ్నలు) మరియు రక్తనమూనా తీసుకొనే సమయము ఒకేసారి అయితే మొదట రక్తనమూనా తీసుకుంటారు తరువాత వైటల్స్, సబ్జక్ట్ యొక్క క్షేమము ఉద్దేశించి అడిగే ప్రశ్నలు మరియు భోజన పక్రియలు చెప్పబడిన క్రమములో ఒకదాని తరువాయు మరొకటి ఉంటాయు.

4.3.15 ప్రతిసారి (ప్రతిపీరియడ్‌లోనూ) రక్తం నమూనా తీసుకుంటారు. ముంజేతి నరం నుంచి చిన్న ప్లాస్టిక్ ట్యూబ్ ద్వారా రక్తం నమూనాలు తీస్తారు. ఏమోక్సిసిలిన్ మోతాదు వేసే ముందుగా మొదటిసారి రక్తం నమూనా తీసుకుంటారు.

4.3.16 ఏమోక్సిసిలిన్ మందును వేసుకున్న తరువాత వరుసగా 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 మరియు 12.0 గంటలకు రక్తం నమూనాలు తీసుకుంటారు.

4.3.17 నమూనా తీసిన ప్రతిసారి 6 మి.లీ. రక్తం తీసుకుంటారు.

4.3.18 రక్తం నమూనా సేకరించటానికి పీలుగ రక్తం గడ్డ కట్టకుండా నివారించడానికి 1.0 మి.లీ. (5 IU/mL) హెపారిన్ (ఇది మానవ శరీరంలో సామాన్యంగా ఉంటుంది) ను ఉప్పు నీటి ద్రావణంతో ఇంజెక్ట్‌చేసి ముంజేతికి ఉన్న చిన్న ప్లాస్టిక్ ట్యూబును నమూనా సేకరించినంత కాలం అలాగే ఉంచడం జరుగుతుంది.

4.3.19 ప్లాస్టిక్ ట్యూబులో రక్తం గడ్డకట్టినచో క్లినికల్ పరిశోధకులు మరియు డాక్టరు సూచిస్తే మరో నరం నుంచి కూడా డిస్ పోసబుల్ స్టెరిలైజ్డ్ సూది ఉపయోగించి రక్తనమూనా తీయవచ్చు.

4.3.20 మొత్తం మీద రెండు సార్లు కలిపి 34(17x2) రక్తనమూనాలు తీస్తారు. స్క్రీనింగ్ లో తీసిన 9 మి.లీ. నమూనా, మందు వడిలిపేసిన 32 మి.లీ., అధ్యయనంలో రెండు పీరియడ్‌లలోనూ తీసిన 204 మి.లీ. మరియు పీరియడ్ 2 అధ్యయనం అనంతం ల్యాబ్ పరీక్షలకు 7 మి.లీ. కలిపి నమూనాగా సేకరించిన రక్తం 254 మి.లీ. మించదు.

4.3.21 మందు మోతాదు వేసుకొనే 48 గంటలముందు నుంచి, కేంద్రంలో వున్న సమయంలోను ప్రతిపీరియడ్‌లోనూ మీరు మద్యం, సిగిరేట్లు, పొగాకుతో తయారుచేసిన ఉత్పత్తులకు దూరంగా ఉండాలి. గ్జాంతీన్ ఉండే (చాక్లెట్లు, టీ, కాఫీ, కోలాపానీయాలు) ఆహారం మరియు పానీయాలను తినకూడదు, తాగకూడదు.

4.3.22 మందుకు / అధ్యయనానికి సంబంధించి వచ్చే ప్రతికూల పరిస్థితులకు క్లినికల్ యూనిట్, సిపిడి లోని డాక్టరుకాని, దగ్గరలో ఉన్న తగిన ఆసుపత్రిలో కాని చికిత్స చేయడం జరుగుతుంది. దీని కోసం మీరు ఖర్చు పెట్టనవసరం లేదు.

4.3.23 మీరు ఆరోగ్యంగా, ప్రతికూల పరిస్థితులకు లోనుకాకుండా ఉన్నట్లయితే అధ్యయనం పూర్తయిన తరువాత (12.0 గంటల రక్తనమూనా ఇచ్చిన తరువాత) ఇంటికి పంపివేస్తారు. ఒకవేళ ప్రతికూల పరిస్థితులు ఉంటే, మీకు తగిన వైద్య చికిత్స చేసి, కోలుకునే వరకూ అబ్జర్వేషన్ లో గమనిస్తూ ఉంచడం జరుగుతుంది.

4.3.24 మీరు ప్రతిసారి (ప్రతిపీరియడ్‌లోను) క్లినికల్ యూనిట్, సిపిడికేంద్రంలో సుమారు 30గంటల పాటు ఉంటారు.

4.3.25 అధ్యయనానికి సంబంధించి ఏదైనా కొత్త సమాచారము లభించినయెడల అలా లభించిన సమాచారమును మీకు తెలుపగలము.

4.3.26 ఇరవై నాలుగు మంది వాలెంటీర్‌లు ఈ అధ్యయనంలో పాల్గొంటారు మరియు నలుగురు వాలెంటీర్‌లు సహకారిగ ఉంటారు.

5 అధ్యయనంలో ప్రమాదాలేమిటి?

ఏమోక్సిల్ భారతదేశంలోను మరియు ఇతర దేశములలో గత కొన్నేళ్ళుగా మార్కెట్ లో లభ్యమగుచున్నది. కాని కొంతమంది మనుషులలో ఎక్కువ కాలం మందు వాడటం వలన దుష్పరిణామాలు కలుగును.

ఒక ఏమోక్సిల్ మాత్ర ఆరోగ్యవంతమైన మానవునికి ఇచ్చినచో ఏమి దుష్పరిణామాలు ఉండవని మేము ముందుగా ఊహించుచున్నాము. ఇది మా మదింపు మాత్రమే, అయితే స్వల్పమైన దుష్పరిణామాలు కలుగవచ్చు.

వాంతి అయ్యేటట్లు అనిపించుట, వాంతులు, విరోచనములు 5% మరియు రక్తహీనతతో కూడిన లేదా Pseudomembranous Colitis (చిన్నప్రేగులకు సంబంధించినటువంటి రుగ్మత).

అతితక్కువగా కలిగే దుష్పరిణామాలు: పిపిధరకాల చర్మ సంబంధ చర్యలు మరియు ఎనాఫిలాక్సిస్ అనే చర్య. కాలేయ సంబంధిత పరీక్షలలో మార్పులు వచ్చుట, కాలేయములో వాపు మరియు పసికర్లు. హిమోగ్లోబిన్ శాతంలో మార్పులు సంబపించుట, తెల్ల రక్తకణాలసంఖ్య

తగ్గుట, పళ్ళయొక్క రంగు మారుట, సిద్రలేమి, ఆదుర్దా, టెన్షన్, మూర్ఛలు, వ్యవహారసరళిలో మార్పు మరియు తల త్రిప్పుతున్నట్లు అనిపించుట.

ముంచేతికి ఉంచిన ట్యూబు ద్వారా రక్తము తీసుకోవటం అనే పద్ధతి వలన ట్యూబు ఉంచిన ప్రదేశములో జిల, వాపు, అసౌకర్యము మరియు ఇన్ ఫెక్షన్ కలుగవచ్చు.

6. అధ్యయనంలో పాలుపంచుకొనడం వల్ల ప్రయోజనాలున్నాయా?

అధ్యయనం వల్ల మీకు ప్రత్యక్ష ప్రయోజనం ఉండదు. అధ్యయనంలో ఇచ్చే మందుల చికిత్స మీకు అవసరం లేదు కనుక ఈ మందుల వల్ల మీకు ప్రయోజనం ఉండదు. ఈ అధ్యయనంలో పాల్గొనటం ద్వారా ఉచితంగా వైద్య పరీక్ష చేయించుకొనవచ్చు. అధ్యయనంలో పాల్గొన్నందుకు ఫీజు (స్వచ్ఛంద కార్యకర్తల నష్టపరిహారం), మందుల పరిశోధనకు తోడ్పడ్డామనే సంతృప్తి మీకు లభిస్తాయి.

7. ఇతర మార్గాలేమిటి?

ఈ అధ్యయనం పరిశోధనకు ఉద్దేశించబడినది. మీకున్న మరో మార్గం అధ్యయనంలో పాల్గొనకుండా ఉండటం.

8. వివరాలూ రహస్యంగా ఉంచుతారా?

అధ్యయనంలో సేకరించిన మీ వైద్య రికార్డులను రహస్యంగా ఉంచుతారు. అధ్యయనానికి సంబంధించిన రికార్డులను నాణ్యతా హామీ కోసం, సమాచార విశ్లేషణ కోసం క్రింది సంస్థలు పరిశీలించవచ్చు.

- సంబంధిత నియంత్రణాధికారులు (ఉదా: యుయస్ ఎఫ్‌డిఎ / యు.కె ఎం.హెచ్.ఆర్.ఎ / డి.సి.జి.ఐ.)
- నియమిత సభ్యులు / పరిశోధకులు : ఎ పి యల్ ఆర్ సి యొక్క క్యు ఎ డి / సి పి డి
- ఎపిఎల్ ఐఆర్‌బి సభ్యులు.
- అందుబాటులో ఉండే రిపోర్టులలో నిర్దిష్ట కార్యకర్తను గుర్తించే సమాచారం ఉండదు.

9. ఆర్థిక నష్టపరిహారం ఎంత?

అధ్యయనంలో పాల్గొన్న రోజులలో మీకు జరిగే వేతన నష్టం మీకు చెల్లించటం జరగదు. అయితే మీరు పొందే అసౌకర్యానికి రూ.2,175/- లు పరిహారంగా చెల్లించటం జరుగుతుంది. అధ్యయనం ముగియకుండా మీరు వైదొలగితే కింది పిధంగా నష్టపరిహారం ఉంటుంది.

పాల్గొను వ్యక్తి గుర్తింపు నెం ..... ఫైనల్

అధ్యయనం నుంచి పైదొలగే కారణం	నష్టపరిహారం
క్లినికల్ పరిశోధకుడు/అధ్యయన సమయంలో ఉండే వైద్యుడు మీ ఆరోగ్యం దృష్ట్యా అధ్యయనం నుంచి తొలగించాలని తీసుకునే వైద్య పరమైన నిర్ణయం	పూర్తిగా చెల్లింపు ఉంటుంది
అధ్యయనం మొదలైన తరువాత మీరు ఇచ్చికంగా పైదొలగినపుడు	పాల్గొన్న నిష్పత్తికి 100% బకాయిలు. (యస్.ఓ.పి నెం. APL-CPD-230-XX లో చెప్పిన పిదంగా ఉంటాయి)
మిమ్మల్ని చూస్తున్న క్లినికల్ పరిశోధకుల/అధ్యయన సమయంలో ఉండే వైద్యుడు అనుమతితో మిమ్మల్ని అధ్యయనం నుంచి దయతో తొలగించినపుడు	పాల్గొన్న నిష్పత్తికి 100% బకాయిలు.
అధ్యయనానికి కావలసిన అంశాలను అతిక్రమించినందుకు, ముందు తీసుకొనకముందు, అంగీకార పత్రంపై సంతకం చేసిన తరువాత, క్లినికల్ పరిశోధకుడు / అధ్యయన సమయంలో ఉండే వైద్యుడు మిమ్మల్ని అధ్యయనం నుంచి తొలగించినపుడు	ఏమీ చెల్లించరు.
క్లినికల్ యూనిట్, సిపిడి నియమాలను ఉల్లంఘించినందుకు క్రమశిక్షణ రాహిత్యానికి మిమ్మల్ని క్లినికల్ పరిశోధకుడు/అధ్యయన సమయంలో ఉండే వైద్యుడు అధ్యయనం నుంచి తొలగించినపుడు	ఏమీ చెల్లించరు.
క్లినికల్ పరిశోధకుడు/అధ్యయన సమయంలో ఉండే వైద్యుడు, మరే ఇతర కరణాల వలన అధ్యయనం నుంచి తొలగించినపుడు లేదా మీరు తొలగినచో	ఐఆర్బి, నిర్ణయం ప్రకారం చెల్లింపు ఉంటుంది

XX - యస్. ఓ. పి యొక్క ప్రస్తుత వర్షన్ నెం.

10. ప్రతికూల పరిస్థితులకు నష్టపరిహార మేమిటి?

క్లినికల్ యూనిట్, ఎపిఎల్, సిపిడి లో ఉన్నపుడు ఎదురయ్యే ప్రతికూల పరిస్థితులకు మీరా హాస్పిటల్ గాని, హైదరాబాద్‌లో దగ్గరలో ఉన్న ఏ సూపర్ స్పెషాలిటీ హాస్పిటల్ లో గాని, మీకు కానీ ఖర్చు లేకుండా వైద్యం చేయడం జరుగుతుంది. తీవ్ర ప్రమాదం సంభవించినపుడు ఎపియల్ ఐఆర్బి సభ్యులు నిర్ణయించిన లేదా నిర్దారించిన భీమా ప్రకారం నిరపరాధ నష్టపరిహారం చెల్లించడం జరుగుతుంది.

11. అధ్యయనంలో పాల్గొంటున్నపుడు నా హక్కులేమిటి?

పరిశోధన కార్యకర్తగా మీహక్కులను, భద్రతను ఎపియల్ సంస్థ ఐఆర్‌బి, ఎపిఎల్-సిపిడి కాపాడతాయి. అంతేకాక అధ్యయన కార్యకర్తగా మీ సమగ్ర భద్రత, హక్కులు, రహస్యాలను కాపాడతామని ఎపిఎల్ సంస్థ రెవ్యూ బోర్డు, ఎపిఎల్-సిపిడి హామీ ఇస్తుంది. అధ్యయనంలో మీరు స్వచ్ఛందంగా పాల్గొంటున్నారు. దీనిలో మీరు పాల్గొనటానికి తిరస్కరిస్తే జరిమానా ఏమీ లేదు. మీరు ఈ అధ్యయనం నుంచి పైదొలగాలనుకుంటే, అధ్యయనం డాక్టరు/పరిశోధకుడు మీతో చర్చించి అధ్యయనం నుంచి సక్రమంగా తొలిగిపోయే మార్గాన్ని మీకు వివరిస్తారు. కారణం చెప్పి, ఏ కారణం కూడా చెప్పకుండా కూడా మీరు అధ్యయనం మధ్యలోపాల్గొనకుండా ఉన్నా ఎపిఎల్-సిపిడితో గాని, దాని సిబ్బందితో గాని మీ సంబంధాలు చెడిపోవని హామీ ఇస్తున్నాం.

12. నేనేం చెయ్యాలి?

మీరు క్లినికల్ యూనిట్, సిపిడి సిబ్బందితో సహకరించాలి. మీరు రాగానే మిమ్మల్ని, మీ సామానును సోదా చేస్తారు. కేంద్రానికి వచ్చిన ప్రతిసారి మీ వ్యక్తిగత వస్తువులను పరీక్షిస్తారు. అధ్యయనంలో పాల్గొన్నప్పుడు మీరు క్లినికల్ యూనిట్, సిపిడి నియమనిబంధనలు పాటించి, అధ్యయన కాలంలో, మీరు కేంద్రంలో నివసించినపుడు, క్రమశిక్షణతో ఉండాలి.

13. మీ అంగీకారం లేకుండా, అధ్యయనం నుంచి పరిశోధకుడు మిమ్మల్ని తొలగించే పరిస్థితులేమిటి?

13.1 మందుకు ప్రతిచర్య వచ్చినపుడు.
13.2 ప్రతికూల సంఘటనలు.
13.3 సహకరించకుండా, ఒడంబడికను అనుసరించనందుకు
13.4 మీకు మాత్రతీసుకొన్న కొంచెం సేపటికే వాంతి అయినచో (ట్రైము క్లినికల్ పరిశోధకుడు నిర్ణయిస్తాడు.)
13.5 మీరు చివరి మూడు రక్తనమూనాలకు లేదా చివరి రక్తనమూనాకు హాజరుకానిచో లేక ఇవ్వనిచో

14. మీరు పాల్గొంటే, అదనంగా మీకు అయ్యే ఖర్చు ఏమిటి?

మీరు పాల్గొన్నందుకు ఎపిఎల్-సిపిడికి మీరు ఏమీ చెల్లించనవరం లేదు. మీ రాకపోకలకు ఖర్చు, భోజనం అన్నిటినీ ఎపిఎల్-సిపిడి భరిస్తుంది. అదనంగా మీరు పొందే అసౌకర్యానికి మా యొక్క SOP No: APL-CPD-230-XX ప్రకారము పరిహారంగా చెల్లించడం జరుగుతుంది.

15. నేనేదైనా అడగాలనుకున్నప్పుడు, సమస్య వచ్చినపుడు నేనెవరిని సంప్రదించాలి?

అధ్యయనం జరుగుతున్నంతకాలం, అధ్యయనానికి సంబంధించిన సమాచారం మీరు స్వేచ్ఛగా పొందవచ్చు. అధ్యయన సమయంలో అత్యవసర వైద్య సేవలు, అత్యవసర ప్రశ్నలకు సమాధానాలు పొందవలసి వస్తే కింద సూచించిన ఎపిఎల్-సిపిడి సిబ్బందిని సంప్రదించవచ్చు.

శ్రీ ఎన్. నాగరాజ్ కుమార్ మొబైల్ నెం. 94401-43138

డాక్టరు సితిన్ కుల్కర్ని, మొబైల్ నెం. 9440053449

చిరునామా : క్లినికల్ యూనిట్,
అరబిందో ఫార్మా లిమిటెడ్ (సిపిడి)
మీరా మల్టీస్పెషాలిటీ హాస్పిటల్
ప్లాట్ నెం. 33, 34, 35
అల్లూరి సీతారామరాజు కాలనీ,
జె.పి. నగర్ కాలనీ ఎదురుగా,
మియాపూర్, హైదరాబాద్-50.
రంగారెడ్డి జిల్లా.
టెలిఫోన్: 91-40-23045809, 91-40-23045709.

మానవ కార్యకర్తగా మీ హక్కులను గురుంచి ప్రశ్నలుంటే ఎపిఎల్ ఐఆర్‌బి చైర్మన్ ను మీరు సంప్రదించవచ్చు.

చిరునామా : జస్టిస్ వై.పి.నారాయణ (రిటైర్డ్)
చైర్మన్, ఎపిఎల్ - ఐఆర్‌బి
ప్లాట్ నెం. 402, పూజాస్ ప్రయిడ్,
ప్లాట్ నెం. 75, శ్రీనగర్ కాలనీ, హైదరాబాద్-500 073.
టెలిఫోన్: 91-40-23743173

పాల్గొను వ్యక్తి గుర్తింపు నెం ..... ఫైనల్

వాలెంటీర్ పిపేచన పూర్వక అంగీకారాన్ని తెలియచేయుచున్న పత్రం

అధ్యయనం పేరు : భారతదేశంలోని అరబిందో ఫార్మా తయారు చేసిన ఏమోక్సిసిలిన్ 500 మి.గ్రా. కాప్సుల్ (పరీక్ష)కు, UK లోని గ్లాక్సోస్మిత్క్లైన్, వారి ఎమోక్సిల్ కాప్సుల్ (రిఫరెన్స్)కు పోలికతోకూడిన జీవతుల్యతాధ్యయనం. ఆరోగ్యవంతులైన, వయోజనులైన 24 (ప్రత్యామ్నాయ) మగ, మానవ వ్యక్తులకు మందు పేరు తెలిపి, రెండు సార్లు వరుసగా, రెండు సమయాలలో ఒకదాని తరువాత ఒకటిగ ఒక మోతాదు మందును నిరాహార పరిస్థితులలో ఇస్తారు.

అధ్యయనం నెంబరు: ఎయమ్ఎక్స్-06/04

పివరణ : నేను పివరించేది ఏమనగా :-

1. పిపేచన పూర్వక అంగీకార పత్రాన్ని చదివాను.
   దానిలోని పిషయాలను పావకాశంగా అవగాహన చేసుకున్నాను. అధ్యయనం గురించి పిన్న తరువాత ప్రశ్నలడిగితే, సంతృప్తికరమైన సమాధానాలు లభించాయి.

2. నా ఇష్ట పూర్వకంగా దీనిలో పాల్గొంటున్నాను.

3. ఏ సమయంలోనైనా అధ్యయనం నుంచి తొలగిపోయే హక్కు నాకు ఉంది.

4. ఈ అధ్యయనం వల్ల కలుగ బోయే ప్రమాదాలు, ప్రయొజనాలు నాకు తెలుసు.

5. ఈ అధ్యయనంలో పాల్గొనటం వల్ల నాకు ప్రత్యక్షంగా ప్రయొజనంలేదని నాకు తెలుసు.

6. నా పైద్య చరిత్రకు సంభంధించి ఏ సమాచారాన్ని నేను దాచలేదు.

7. నాకు చెప్పిన కారణాల వల్ల, అధ్యయనం నుంచి నన్ను ఏ సమయంలోనైనా నా అనుమతి లేకుండా తొలగించవచ్చు.

8. ఈ అధ్యయనం ప్రయోగానికి సంబంధించినదని, మరియు దీనిలో పాల్గొనటంవలన నాకు ఏ పిధమైన పైధ్య సంబంధిత లబ్ధి చేకూరదని తెలుసు.

9. జీతం నష్టానికి ఎపిఎల్ -సిపిడి ఏ రకమైన నష్ట పరిహారం చెల్లించదు.

10. ప్రతి సారి కేంద్రం నుంచి బయటికి వెళ్ళే వరకు వారిచ్చిన గుర్తింపు కార్డును, బట్టలను ధరించి ఉంటాను.

వాలెంటీర్ సంతకము..... తేది.....

...ky

పాల్గొను వ్యక్తి గుర్తింపు నెం ..... ఫైనల్

11. ఏదైనా ప్రమాదం సంభవించినపుడు, ఎపిఎల్ ఐఆర్‌బి బోర్డు నిర్ణయించిన నిరపరాధ నష్టపరిహారం నాకు లభిస్తుంది.

12. మందు / అధ్యయన సంబంధిత ప్రతికూలతలకు నాకు ఖర్చు లేకుండా అరబిందో ఫార్మా లి మిటెడ్ (సిపిడి) చికిత్స చేయిస్తుంది.

13. ఏమైనా ప్రశ్నలు వేయాలనుకున్నపుడు, అత్యవసర పరిస్తుతులలో ముందు పుటలలో సూచించిన వ్యక్తులను సంప్రదించవచ్చు.

14. అధ్యయనంలో పాల్గొనటానికి అంగీకారాన్ని తెలుపుతున్నట్లుగా నా సంతకం లేదా వేలి ముద్ర సిద్ధరిస్తుంది.

15. నాకు తెలిసిన సమాచారాన్ని ఆధారం చేసుకుని నా అంగీకారాన్ని తెలుపుతున్నాను.

16. సంతకముతో కూడిన పిపేచనాపూర్వక అంగీకార పత్రం యొక్క ఒక ప్రతి నాకు ఇవ్వబడును అని తెలుసు.

కార్యకర్త పేరు :		పక్షపాతంలేని సాక్షి పేరు : పక్షపాతంలేని సాక్షి అడ్రస్ :	
సంతకంలేదా వేలి ముద్ర	తేది	సంతకం	తేది

గమనిక: పక్షపాతంలేని సాక్షి సంతకం నిరక్షరాశ్యులైన వాలెంటీర్ కు మాత్రమే సంభందించినది.

ఎపిఎల్ (సిపిడి): అరబిందో ఫార్మా లి మిటెడ్ (క్లినికల్ ఫార్మకాలజీ డిపార్ట్మెంట్)
ఐ ఆర్ బి: ఇన్స్టిట్యూషనల్ రివ్యూ బోర్డ్

అంగీకారాన్ని తీసుకున్నవారు: .....

క్లినికల్ పరిశోధకుని / డాక్టరు సంతకం..... తేది.....

వాలెంటీర్ సంతకము..... తేది.....

Study no.: Amx-06/04

Test Drug (T): Amoxicillin capsules containing amoxicillin as trihydrare equivalent to 500 mg of Amoxicillin manufactured by Aurobindo Pharma Ltd., India.
Batch no.: ANBCB 4001; Mfg Date:06/2004; Exp. Date:05/2006

Reference Drug (R): Amoxil capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin manufactured by GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK).
Batch no.: 85484 A; Mfg Date: Not Available; Exp. Date: 12/2006

Subject ID	Sequence	Period I	Period II
01	1	R	T
02	2	T	R
03	1	R	T
04	2	T	R
05	2	T	R
06	1	R	T
07	1	R	T
08	2	T	R
09	2	T	R
10	1	R	T
11	1	R	T
12	2	T	R
13	1	R	T
14	2	T	R
15	1	R	T
16	2	T	R

09/11/04

Prepared by: P.Pramod Kumar Reddy (Biostatistician)

09/11/04

Approved by: N. Nagarajkumar (Principal Investigator)

Study no.: Amx-06/04

Test Drug (T): Amoxicillin capsules containing amoxicillin as trihydrare equivalent to 500 mg of Amoxicillin manufactured by Aurobindo Pharma Ltd., India.

Batch no.: ANBCB 4001; Mfg Date:06/2004; Exp. Date:05/2006

Reference Drug (R): Amoxil capsules containing Amoxicillin as trihydrate equivalent to 500 mg of Amoxicillin manufactured by GlaxoSmithKline, UK (SmithKline Beecham Pharmaceuticals, UK).

Batch no.: 85484 A; Mfg Date: Not Available; Exp. Date: 12/2006

Subject ID	Sequence	Period I	Period II
17	1	R	T
18	2	T	R
19	1	R	T
20	2	T	R
21	2	T	R
22	1	R	T
23	1	R	T
24	2	T	R
25	2	T	R
26	1	R	T
27	1	R	T
28	2	T	R

07/11/04

Prepared by: P.Pramod Kumar Reddy (Biostatistician)

07/11/04

Approved by: N. Nagarajkumar (Principal Investigator)