

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-357/S019

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

copy /S/ 12-9/11

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Clinical Pharmacology & Biopharmaceutics
(HFD 860/870/880)
Tracking/Action Sheet for Formal/Informal Consults

From: Xiaoxiong (Jim) Wei, M.D., Ph.D.

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified IND/NDA submission

DATE: 9/5/00

IND No.: N/A
Serial No.:

NDA No.
20-357

Document ID:

DATE OF DOCUMENT
02/15/00

NAME OF DRUG
[Glucophage/metformin]

PRIORITY CONSIDERATION
N/A

Document Type and Sequence
No.: SE5-019

Date of informal/Formal Consult: N/A

NAME OF THE SPONSOR: [Bristol-Myers Squibb]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS ASSIGNMENT

- | | | |
|--|--|--|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input checked="" type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> PHASE IV RELATED | | [Study report for pediatric exclusivity] |

REVIEW ACTION

- NAI (No action indicated)
- | | | |
|---|--|---|
| <input type="checkbox"/> E-mail comments to:
<input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox
<input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | <input type="checkbox"/> Oral communication with
Name: []
<input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: [] | <input checked="" type="checkbox"/> Formal Review/Memo (attached)
<input type="checkbox"/> See comments below
<input type="checkbox"/> See submission cover letter
<input type="checkbox"/> OTHER (SPECIFY BELOW):
[] |
|---|--|---|

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS:
See review

SIGNATURE OF REVIEWER: /S/ /S/
SIGNATURE OF TEAM LEADER
A 20-357 [orig., 1 copy], HFD 510 [Weber], HFD 850 [Lesko], 870 [Ahn, Wei, Huang], CDR;

Date 9/5/00
Date 9/8/00
Code:AE

pediatric subjects with Type 2 diabetes mellitus. A total of 32 qualified subjects were evaluated for metformin pharmacokinetics after at least one week on 1000 mg metformin daily (500 mg BID with morning and evening meals) in order to reach steady state prior to pharmacokinetic sampling. Serial plasma samples were obtained over a period of 11 hours and were analyzed for metformin using a method. Urine samples were obtained over the 11 -hour dosing interval and analyzed for metformin by method. Note: the assay and quality control used in this study are fine to this reviewer).

The pharmacokinetic data from 26 out of 32 enrolled subjects were included in summary statistics of pharmacokinetic variables. Data from 6 subjects were excluded: 3 subjects were misdosed; 2 subjects had extremely low plasma metformin concentrations; and 1 subject had only 4 hours plasma concentration data.

The pharmacokinetic parameters were determined using a validated non-compartmental analysis protocol. Metformin pharmacokinetic parameters are summarized in the following table:

Parameter	Arithmetic Mean (SD) (N=26)
C _{max} (µg/mL)	0.73 (0.20)
AUC(TAU) (µg.hr/mL)	4.49 (1.15)
T _{max} (hr)	2.0 (1.0, 4.0)
T-HALF (hr)	3.7 (0.6)
%UR	43.4 (12.4)
CLR (mL/min)	648.0 (182.6)

No gender-related difference in pharmacokinetics was seen. The mean C_{max} and AUC(TAU) were 0.70 µg/mL and 4.38 µg.h/mL for females (n = 16) and 0.77 µg/mL and 4.66 µg.h/mL for males (n = 10).

The sponsor compared this pediatric data with the pharmacokinetic profile of metformin found in a previous 28 doses steady state pharmacokinetic study in adult patients in the following table:

Subject Group	AUC (µg.hr/ml)	C _{max} (µg/ml)	T _{1/2} (hrs)
Pediatric Subjects (aged 12 – 16 yrs) 500 mg BID for 7 days	4.49 (±1.15)	0.73(±0.20)	3.7(±0.60)
Adult Subjects 500 mg BID for 14 days	8.30 (±2.20)	1.22(±0.34)	4.1(±0.69)

The exposure to metformin was approximately half of that found in adults in a separate study under the same dosing regimen. No gender-related difference was seen. The renal clearance of metformin was 648 ml/min in this pediatric population and is approximately 18% greater than the reported value of renal clearance in adults (550 ml/min) with type 2 diabetes. The sponsor stated that the higher renal clearance and lower extent of absorption can partially explain the lower exposure to metformin in pediatric subjects observed in this study.

Reviewer's Comment (To be sent to the firm):

This pharmacokinetic study fulfilled the proposed requirement for pediatric exclusivity described in the letter issued by the Agency dated 06-09-99, amended 02-09-00. The study results observed in pediatric patients showed that the pharmacokinetic parameters were drastically different from those found in adult patients. The patients were relatively new to treatment and took medications at home. This reviewer suspects compliance in this study. Particularly, 6 out of 32 enrolled patients was excluded for data analysis because of misdose, too low plasma concentrations and only partial plasma data availability, etc. Therefore, it is suggested that an additional, confirmatory single dose pharmacokinetic study of metformin be conducted in pediatric and adult patients

LABELING COMMENT:

Consequently _____

Therefore, the proposed _____ should be deleted. No revision on pharmacokinetics should be made under Pediatric subsection.

/S/

9/8/00

Xiaoxiong (Jim) Wei, M.D., Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

/S/

9/8/00

CC: NDA 20-357 (orig., 1 copy), HFD-510 (Weber), HFD-850 (Lesko), HFD-870 (Wei, Ahn, Huang), CDR.

Code: AE

Attached: (1) study synopsis, (2) assay quality control, (3) individual PK data summary, (4) proposed labeling.

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Final Study Report: CV138-038-PK

28 January 2000

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

FINAL REPORT SYNOPSIS

TITLE OF STUDY: A Study of the Pharmacokinetic Profile of Metformin Hydrochloride in Pediatric Subjects; a Substudy of a Multicenter, Randomized, Open Label, Parallel Study of the Pharmacokinetics, Safety, and Efficacy of Metformin Hydrochloride Plus Insulin Compared to Insulin Monotherapy for the Treatment of Pediatric Subjects with Type 2 Diabetes Mellitus

INVESTIGATOR: Multicenter (10 centers; see Appendix 4.0)

STUDY CENTER: Multicenter (10 centers; see Appendix 4.0)

PUBLICATIONS: None

STUDY PERIOD: 04 November 1998
09 December 1999

CLINICAL PHASE: III

OBJECTIVES:

The objective of this study was to establish the pharmacokinetic profile of metformin in pediatric subjects with Type 2 diabetes after receiving metformin (500 mg BID) plus insulin for at least one week.

METHODOLOGY:

The pharmacokinetic profile of metformin was studied in subjects enrolled in a multicenter, open label, randomized, parallel study of pediatric subjects with Type 2 diabetes mellitus. Twenty-nine (29) qualified subjects who were randomized to receive metformin plus insulin therapy were evaluated for metformin pharmacokinetics after at least one week on 1000 mg metformin daily (500 mg BID with morning and evening meals) in order to reach steady state prior to pharmacokinetic sampling. An additional three subjects qualified for inclusion in the PK substudy and were automatically assigned to the metformin plus insulin therapy.

Serial plasma samples were obtained over a period of 11 hours and were analyzed for metformin using a Urine samples were obtained over the 11-hour dosing interval and analyzed for metformin by

NUMBER OF SUBJECTS:

A total of 32 subjects were enrolled and completed the study.

MAIN CRITERIA FOR INCLUSION:

Males and females (non-nursing, non-pregnant, and if sexually active, practicing an effective method of birth control) ≥8 - ≤16 years of age at screening with a previously or newly established diagnosis of Type 2 diabetes mellitus were eligible for the study if they met the following inclusion criteria: either FPG levels ≥180 mg/dL and HbA_{1c} ≥7.0%, or current treatment with insulin at screening, and stimulated C-peptide ≥1.5 ng/mL (90 min after standardized Sustacal® challenge), serum creatinine ≤1.0 mg/dL or a normal creatinine clearance rate, BMI ≥25 kg/m², absence of onset of diabetic ketoacidosis <8 weeks prior to screening, off all oral hypoglycemic therapy except troglitazone ≥28 days prior to randomization (off troglitazone ≥6 months prior to randomization), and subject and subject's parent or legal guardian had signed a patient informed consent.

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Final Study Report: CV138-038-PK

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TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Dose and Appearance	Product Number	Route	Batch Number
Glucophage [®] 500 mg Tablets, round	NDC 0087-6060-05	Oral	508BKV

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

There was no reference therapy for this study.

DURATION OF TREATMENT:

Metformin (500 mg BID) plus insulin treatment was scheduled to last for at least one week prior to pharmacokinetic analysis.

CRITERIA FOR EVALUATION:

Serial plasma and urine samples for pharmacokinetic analysis were collected at various time points over an 11-hour period after the morning dose on the day of PK sampling. Maximum observed concentration after the dose (C_{max}), time required to reach C_{max} (T_{max}), area under the concentration versus time curve over a dosing interval ($AUC_{[TAU]}$), terminal elimination half-life (T_{-HALF}), renal clearance (CLR) and percent of dose excreted unchanged in the urine over a dosing interval (%UR) of metformin were analyzed. Safety for this substudy was assessed by monitoring adverse events from randomization through the end of the PK visit.

STATISTICAL METHODS:

Sample Size:

The proposed sample size of 24 subjects was to provide at least 95% confidence that the estimated AUC and C_{max} would be within 11% and 13%, respectively, of their true population values. These calculations were based on the assumptions that the standard deviation for $\log(AUC)$ is 0.247 and for $\log(C_{max})$ is 0.294 based on a previous adult pharmacokinetic study. Data from 26 subjects were included in the PK summary statistics.

Statistical Methods:

Subject demographics and diabetes-related laboratory data were summarized. Summary statistics, as well as geometric means and the 95% confidence intervals of $AUC_{[TAU]}$ and C_{max} are provided.

Analysis:

All evaluable pharmacokinetic data from 26 subjects were included in summary statistics of pharmacokinetic variables. Data from 6 subjects were considered not evaluable: 3 subjects were misdosed; 2 subjects had extremely low plasma metformin concentration; and 1 subject had only 4 hours plasma concentration data. All available data from all subjects who had taken at least one dose of study medication were included in the analysis of safety.

PHARMACOKINETIC RESULTS:

The pharmacokinetic results were determined using a validated noncompartmental analysis protocol. Metformin pharmacokinetic parameters are summarized in the following table:

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Final Study Report: CV138-036-PK

28 January 2000

Parameter	Arithmetic Mean (SD) (N=26)
C _{max} (ng/mL) ^a	728.7 (199.7)
AUC(TAU) ^b (ng.hr/mL)	4487.7 (1150.3)
T _{max} (hr)	2.0 (1.0, 4.0) ^a
T-HALF (hr)	3.7 (0.6)
%UR	43.4 (12.4)
CLR (mL/min)	648.0 (182.6)

^a The corresponding values in adults were 1222 ng/mL and 8303 ng.hr/mL in a separate study.
^b Median (Range)

No gender-related difference in pharmacokinetics was seen. The mean C_{max} and AUC(TAU) were 700.6 ng/mL and 4380.4 ng.hr/mL for females and 773.8 ng/mL and 4659.3 ng.hr/mL for males.

SAFETY AND TOLERABILITY RESULTS:

A total of 20 adverse events were reported by 12 (37.5%) of the 32 enrolled subjects. The most common adverse event reported in this pediatric PK substudy was diarrhea, which occurred in 12.5% of the subjects. With one exception, all non-serious adverse events were mild or moderate; only one event was reported as severe, a case of diarrhea. Only one subject experienced a serious adverse event, a hospitalization for cellulitis, but the event was considered unlikely to be related to metformin. In summary, metformin plus insulin treatment was well tolerated by the pediatric subjects in this PK substudy. The type of adverse events reported by the pediatric subjects that were considered drug related were not different from those reported by adults taking metformin.

CONCLUSIONS:

Metformin at 500 mg BID was well tolerated by the pediatric subjects in this PK substudy. The drug was rapidly absorbed and rapidly eliminated in this population. The exposure to metformin was approximately half of that found in adults in a separate study under the same dosing regimen. No gender-related difference was seen.

DATE OF REPORT: 28 January 2000.

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2. ASSAY VALIDATION AND QUALITY CONTROL DATA

Final Study Report: CV138-038-PK

28 January 2000

11 PHARMACOKINETIC/PHARMACODYNAMIC RESULTS

11.1 Assay Performance

A total of 7 analytical runs were required for analysis of metformin in plasma. Summaries of standard curve parameters and mean QC data for metformin in plasma are presented in Tables 11.1A and 11.1B, respectively. The corresponding data for metformin in urine are provided in Tables 11.1C and 11.1D, respectively.

Table 11.1A Standard Curve Summary for Plasma Samples

Run Date	Curve Number	Slope	Intercept	R-Squared	LLQ (ng/mL)	ULQ (ng/mL)
26-Feb-1999	1					
05-Apr-1999	2					
28-May-1999	3					
23-Jun-1999	4					
19-Aug-1999	5					
11-Oct-1999	6					
17-Dec-1999	14					
Mean		0.001076	-0.002650	0.9986		
S.D.		0.000054	0.001778	0.0018		
%CV		5.0	67.1	0.2		
n		7	7	7		

CV138-038-PK

Source: Appendix 11.1

Table 11.1B Quality Control Summary for Plasma Samples

Nominal Conc.	Low (50.000 ng/mL)	Mid (500.000 ng/mL)	Mid (2000.000 ng/mL)	High (10000.000 ng/mL)
Mean Observed Conc.	54.172	500.907	2014.984	10524.778
%Dev	8.3	0.2	0.7	5.2
Between Run Precision (%CV)	7.6	0.0	0.0	4.5
Within Run Precision (%CV)	17.1	4.7	5.5	1.8
Total Variation (%CV)	18.7	4.5	5.3	4.9
n	14	14	14	4
Number of Runs	7	7	7	2

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Source: Appendix 11.1

Table 11.1C Standard Curve Summary for Urine Samples

Run Date	Curve Number	Slope	Intercept	R-Squared	LLQ (µg/mL)	ULOQ (µg/mL)
08-Mar-1999	7					
09-Mar-1999	8					
25-Mar-1999	9					
09-Jul-1999	10					
07-Oct-1999	11					
20-Dec-1999	13					
Mean		0.093330	-0.001799	0.9987		
S.D.		0.018489	0.006782	0.0012		
%CV		19.8	-377.0	0.1		
n		6	6	6		

CV138-038-PK

Source: Appendix 11.1

Table 11.1D Quality Control Summary for Urine Samples

Nominal Conc.	Low (2,000 µg/mL)	Mid (10,000 µg/mL)	Mid (20,000 µg/mL)	High (100,000 µg/mL)
Mean Observed Conc.	1.937	9.673	19.452	99.239
%Dev	-3.2	-3.3	-2.7	-0.8
Between Run Precision (%CV)	6.3	3.4	0.0	10.4
Within Run Precision (%CV)	9.0	10.9	4.1	6.0
Total Variation (%CV)	11.0	11.5	3.8	11.9
n	18	18	18	18
Number of Runs	6	6	6	6

CV138-038-PK

Source: Appendix 11.1

The plasma standard curves had R-squared values of ≥ 0.9946 . The overall between- and within-run variability of the analytical QCs in plasma was less than 17.1%. The relatively high %CV for within run precision was due to one QC sample in run 14 which deviated from the nominal concentration by more than 73%. The mean observed concentrations of the analytical QC samples in plasma deviated less than 8.4% from the nominal values. The urine standard curves had R-squared values of ≥ 0.9967 . The overall between- and within-run variability of the analytical QCs in urine was less than 11% RSD. The mean observed concentrations of the analytical QC samples in plasma deviated less than 3.4% from the nominal values. Data from individual analytical runs

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3. INDIVIDUAL PK DATA

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Table 8.3A Baseline Demographic Characteristics, All Enrolled Subjects

Characteristics	All Enrolled Subjects (N=32)
Gender n(%)	
Male	10 (31.3)
Female	22 (68.8)
Age (years)	
Mean (SD)	14.0 (1.7)
Median	14.5
Range	10, 16
Race N (%)	
White	5 (15.6)
Black	22 (68.8)
Asian/Pacific Islander	1 (3.1)
Hispanic/Latino	4 (12.5)
Weight (kg)	
Mean (SD)	98.4 (23.6)
Range	58.7, 181.4
Height (cm)	
Mean (SD)	166.5 (9.7)
Range	141.9, 183.6
Body Mass Index (kg/m ²)	
Mean (SD)	35.5 (8.1)
Range	26.0, 67.5

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Source: Appendix 8.3A

Reference: Supplemental Table S.8.3A

Individual subject Type 2 diabetes metabolic parameters are listed in Appendix 8.3B and summarized in Table 8.3B.

Table 8.3B Baseline Diabetes Characteristics, All Enrolled Subjects

Characteristics	All Enrolled Subjects (N=32)
HbA _{1c} (%)	
Mean (SD)	9.1 (3.2)
Median	8.3
Range	
FPG (mg/dL)	
Mean (SD)	183.3 (106.7)
Median	146.0
Range	
Stimulated C-peptide (ng/mL)	
Mean (SD)	5.9 (2.9)
Median	6.1
Range	

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Source: Appendix 8.3B

Reference: Supplemental Table S.8.3B

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Table 11.2B Summary of Individual and Mean Pharmacokinetic Parameters of Metformin

SUBJ	Age	C _{MAX} (NG/ML)	T _{MAX} (H)	AUC (TAU) (NG H/ML)	T-1/2 (H)	CLR (ML/MIN)	V _{DR}
STUDY CENTER = 03							
001	15						
003	16						
012	13						
007#	12						
020	13						
018#	15						
027	16						
019	15						
034	12						
STUDY CENTER = 04							
001	12						
005	16						
004#	15						
006	14						
010	13						
STUDY CENTER = 07							
001	16						
004	13						
STUDY CENTER = 08							
004	15						
STUDY CENTER = 12							
005	15						
STUDY CENTER = 16							
001	12						
004	16						
007	12						
002	15						
005	15						
010#	10						
STUDY CENTER = 18							
002#	12						
003#	12						
004	16						
STUDY CENTER = 26							
009	16						
011	16						
008	13						
012	13						
015	13						
MEAN		728.72	2.00*	4487.67	3.71	647.95	43.38
SD		199.70	(1.00, 4.00)	1150.26	0.63	182.58	12.41
N		26	26	26	26	26	26

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Source: Appendix 11.2

* MEDIAN (MINIMUM, MAXIMUM)

Subjects excluded from calculation of means (see Section 8.2).

* Subject received metformin 1000 mg on day of PK sampling; V_{DR} was calculated based on 500 mg dose.

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Table 11.2C Summary of Mean Pharmacokinetic Parameters of Metformin

Parameter	Arithmetic Mean (SD) (N=26)
C _{max} (ng/mL)	728.7 (199.7)
AUC(TAU) ^a (ng·hr/mL)	4487.7 (1130.3)
T _{max} (hr)	2.00 (1.0, 4.0) ^b
T-HALF (hr)	3.7 (0.6)
%UR	43.4 (12.4)
CLR (mL/min)	648.0 (182.6)

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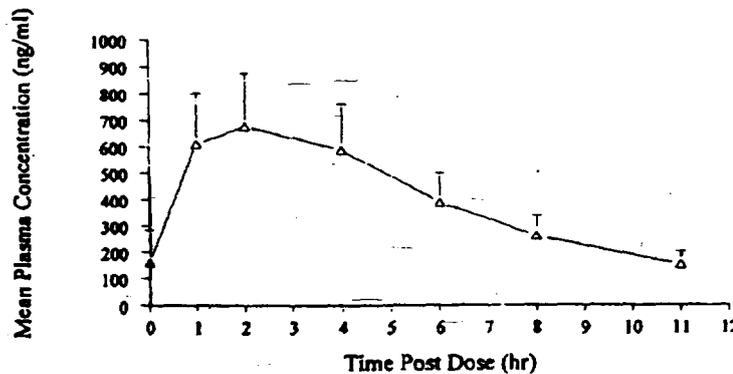
Source: Appendix 6.3.2, Table S.1

^a Area under the plasma concentration-time curve over one dosing interval.

^b Median (Range)

No gender-related difference in pharmacokinetics was seen. The mean C_{max} and AUC(TAU) were 700.6 ng/mL and 4380.4 ng·h/mL for females and 773.8 ng/mL and 4659.3 ng·h/mL for males, respectively (data provided in Appendix 6.3.2, Table S.3).

Figure 11.2A Mean (SD) Plasma Metformin Concentrations over the Dosing Interval



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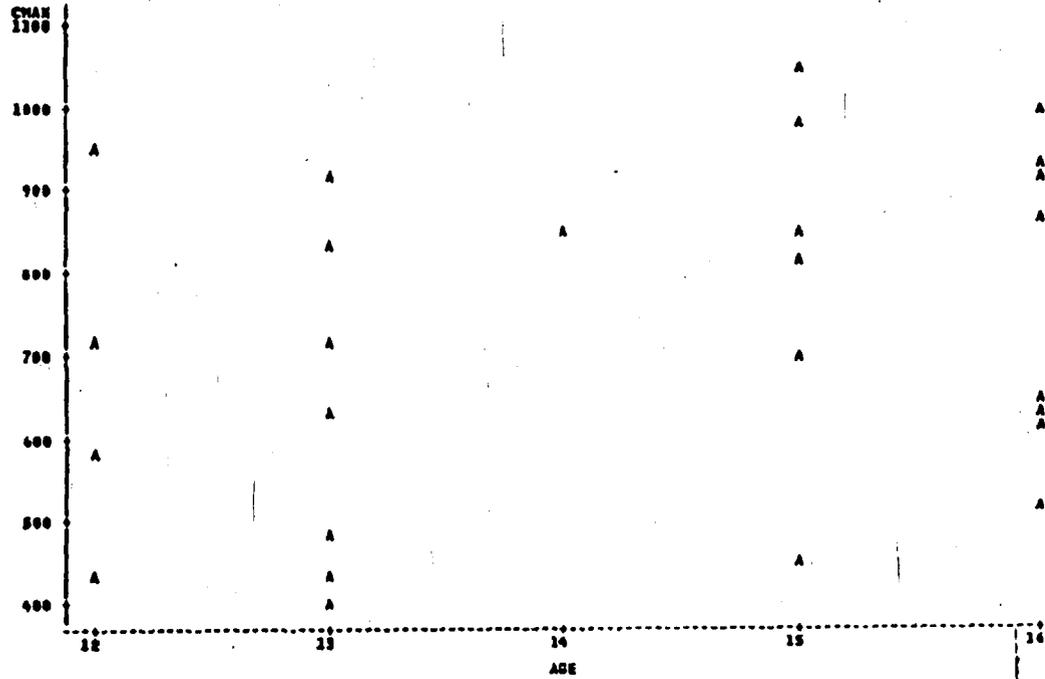
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PROTOCOL CV136-038

STATISTICAL REPORT

Appendix 4.3.2
Supplemental Figure S.1
Scatter Plots for Metformin Pharmacokinetic Parameters Versus Age in Pediatric Subjects
Plot of CMAXAGE. Legend: A = 1 obs, B = 2 obs, etc.



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RUN DATE: 10JAN88

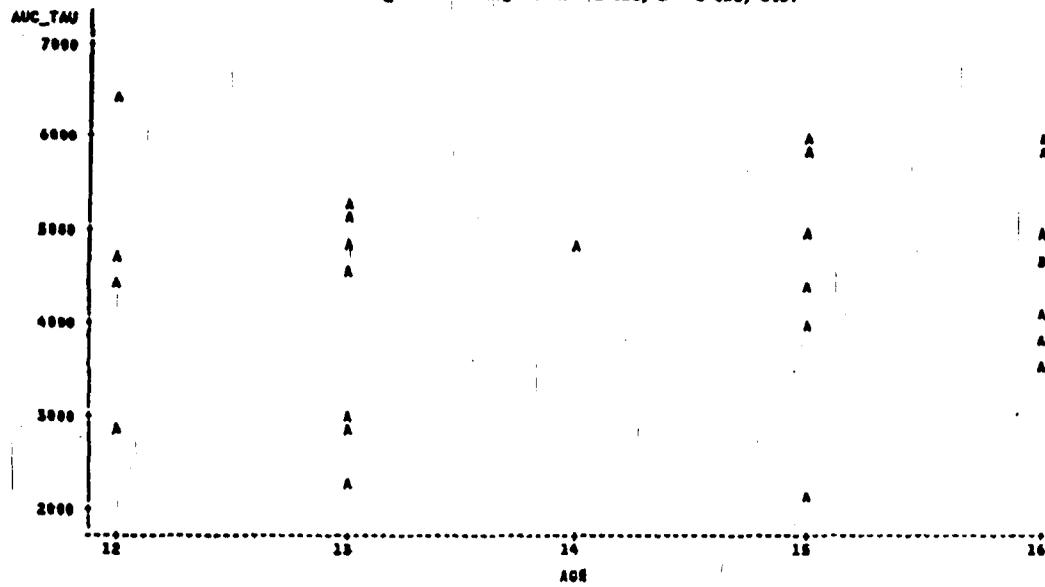
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ND A20-357-SES-019-Metformin-PEDEX-021 500.doc

PROTOCOL CV138-828

STATISTICAL REPORT

Appendix 6.3.2
Supplemental Figure 2.1
Scatter Plots for Metformin Pharmacokinetic Parameters Versus Age in Pediatric Subjects
Plot of AUC_TAU. Legend: A = 1 obs, B = 2 obs, etc.



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PROGRAM: _____

RUN DATE: 10JAN80

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Labeling

