Table JMAA.2. **Dose Proportional Assessments for $AUC_{0-\infty}$ and C_{max} from Power Model**

	Power Model	
Parameter	**Slope (90% CI)**	**DP Ratio**
$AUC_{0-\infty}$ (BSA normalized dose)	1.12 (0.98, 1.25)	2.43
C_{max} (BSA normalized dose)	1.06 (0.93, 1.20)	3.14
$AUC_{0-\infty}$ (total dose)	1.10 (0.95, 1.24)	2.54
C_{max} (total dose)	1.02 (0.86, 1.17)	3.67

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from the start of infusion through infinity; BSA = body surface area; CI = confidence interval; C_{max} = maximum plasma concentration; DP = dose proportionality.

Table JMAA.3. **Dose Proportional Assessments for $AUC_{0-\infty}$) and C_{max} from Power Model with Age as a Covariate**

	Power Model	
Parameter	**Slope (90% CI)**	**DP Ratio**
$AUC_{0-\infty}$ (BSA normalized dose)	1.11 (0.99, 1.23)	2.61
C_{max} (BSA normalized dose)	1.06 (0.93, 1.20)	3.10

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from the start of infusion through infinity; BSA = body surface area; CI = confidence interval; C_{max} = maximum plasma concentration; DP = dose proportionality.

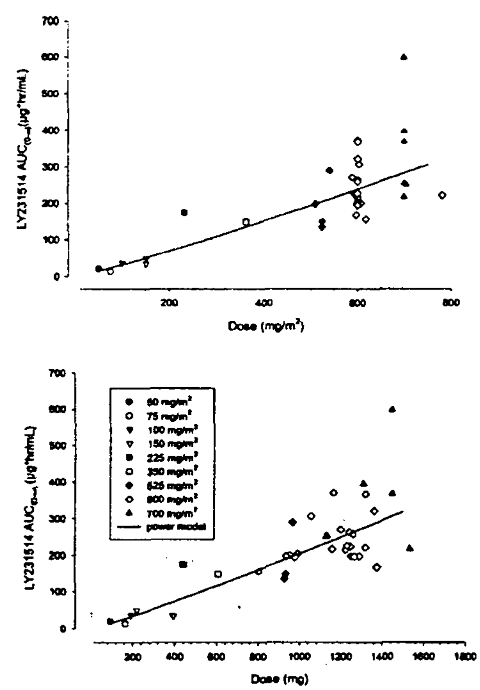

Figure JMAA.4. **Relationship between $AUC_{0-\infty}$ with dose and body surface area normalized dose.**

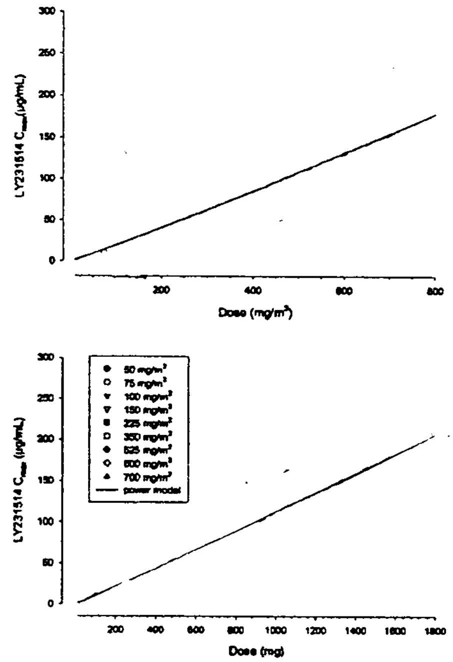

Figure JMAA.5. Relationship between C_{max} with dose and body surface area normalized dose.

Table JMAA.4. Results from Fitting Power Model to Neutrophil Nadir and Platelet Counts Against $AUC_{0-\infty}$ and C_{max}

	Neutrophil Nadir Counts	
	$AUC_{(0-\infty)}$	C_{max}
Slope (90% CI)	-3.53 (-5.14, -1.92)	-2.48 (-4.52, -0.44)
Fold reduction in counts when doubling exposure (90% CI)	12 (4, 35)	6 (1.4, 23)
	Platelet Nadir Counts	
	$AUC_{(0-\infty)}$	C_{max}
Slope (90% CI)	-2.31 (-3.23, -1.40)	-0.64 (-1.94, 0.65)
Fold reduction in counts when doubling exposure (90% CI)	5 (2.6, 9)	1.6 (0.64, 3.8)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from the start of infusion through infinity; BSA = body surface area; CI = confidence interval; C_{max} = maximum plasma concentration.

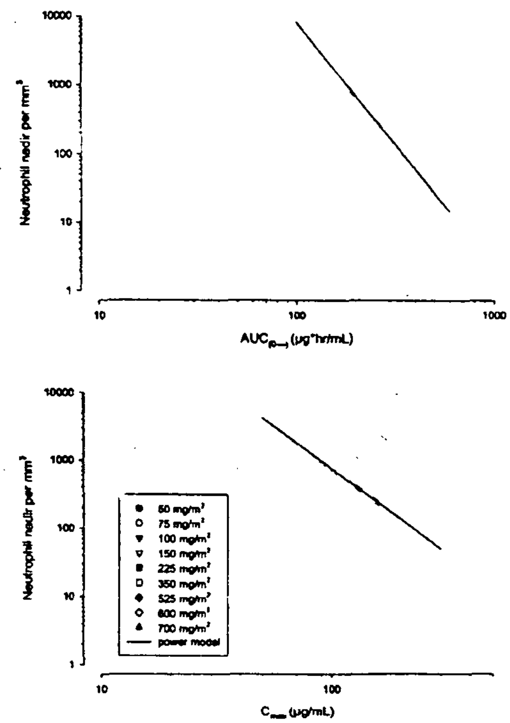

Figure JMAA.6. Relationship between $AUC_{0-\infty}$ and C_{max} with neutrophil nadir after first cycle.

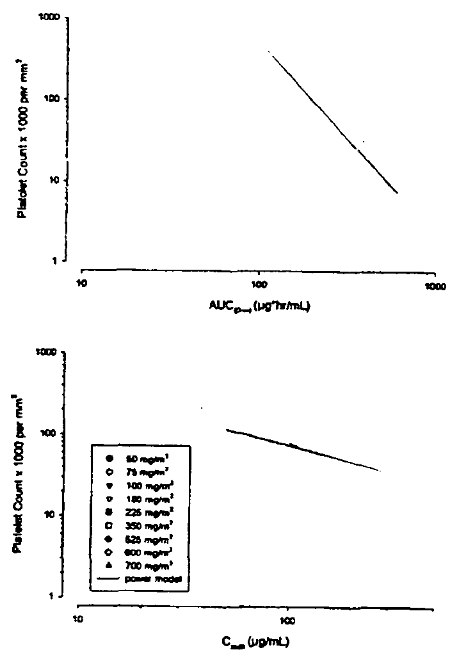

Figure JMAA.7. Relationship between $AUC_{0-\infty}$ and C_{max} with platelet after first cycle.

CL dependent upon age. As age increases, Cl decreases
Neutrophil and platelets decrease with increasing exposure, as AUC increases from 525 mg/m2 dose upwards.
AUC and Cmax are dose-proportional.

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7. BP0001
Phase 1 MTA daily x 5days
Objective: Pk of MTA
Starting dose 0.2 mg/m2, dose escalation
38 patients(19/19)

Table BP00.1. Summary of Patient Demographics

Gender	Statistic	Age (yr)	Body Weight (kg)	Body Surface Area (m^2)[1]
males	mean	59	68.1	1.80
	min	33	44.9	1.43
	max	72	96.6	2.26
	CV%	19	20	12
females	mean	56	60.2	1.60
	min	42	41.5	1.37
	max	71	79.0	1.86
	CV%	16	19	9.1

1 Body surface area obtained from case report form

MTA formulation: — powder, 100 or 500 mg/vial
MTA analysis: — ng/ml
Sampling: 12 samples over 24 hrs on days 1 and 5, trough samples on days 2, 3,4. Urine collection on day 1.

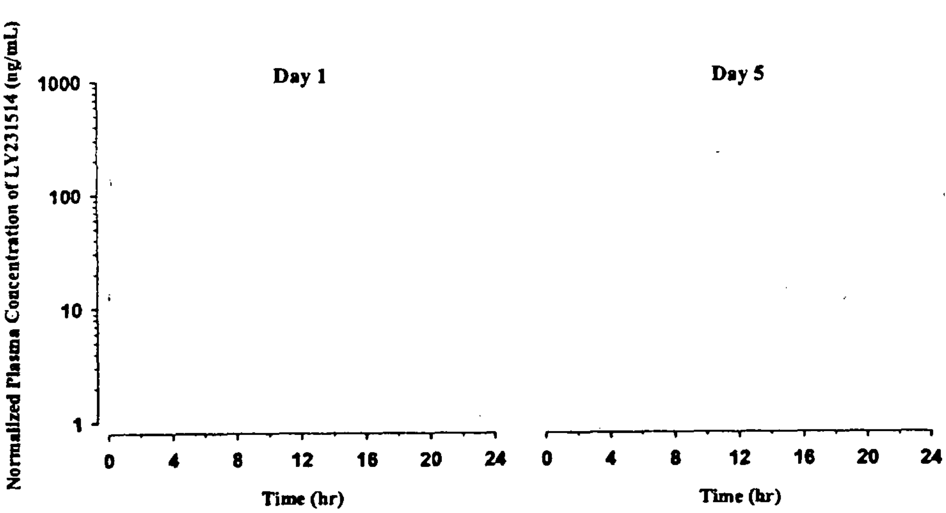


Figure BP00.1. **Individual plasma LY231514 concentration time-profiles on Days 1 (n=29 patients) and 5 (n=23 patients) normalized to a 4 mg dose.**

Table BP00.3. Mean LY231514 Pharmacokinetic Parameters (Day 5)

Parameter	Arithmetic Mean (CV as %) Dose (mg/m²)									
	0.2 (n=3)	0.4 (n=2)[a]	0.52 (n=2)[a]	0.78 (n=1)	1.2 (n=1)	1.8 (n=4)	2.3 (n=1)	3 (n=2)[a]	4 (n=3)	5.2 (n=1)
C_{max} (ng/mL)	64.6 (52%)	44.3 – 59.8	50.3 – 72.0	120	112	312 (36%)	521	472 – 802	682 (33%)	945
$AUC_{0-\infty}$ (ng•hr/mL)	41.0 (83%)	47.2 – 65.0	28.8 – 46.4	98.8	51.3	305 (42%)	384	837 – 1260	591 (32%)	779
T_{max} (hr)[a]	0.08 – 0.22	0.08 – 0.25	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
CL_p (mL/min)	217 (59%)	169 – 194	345 – 434	211	623	188 (59%)	191	68.6 – 95.5	233 (28%)	159
CL_p (mL/min/m²)	123 (64%)	103 – 142	186 – 299	132	390	123 (65%)	99.5	39.4 – 59.7	122 (35%)	111
V_{ss} (L)	10.2 (36%)	11.8 – 22.9	16.3 – 16.4	12.4	19.0	14.0 (23%)	13.8	13.1 – 13.7	17.3 (22%)	12.4
V_{ss} (L/m2)	5.75 (43%)	8.59 – 13.8	8.87 – 11.2	7.75	11.9	9.04 (25%)	7.20	7.88 – 8.17	9.16 (33%)	8.69
$t_{1/2}$[b] (hr)	0.8	0.7 – 2.0	0.6	0.8	0.4	1.0	1.2	2.2	1.2	1.2

[a] both values are reported when n=2

[b] harmonic mean

Urine concentrations were BQL

Power model for dose proportionality

$X = \alpha Y^{\beta}$

Table BP00.2. Mean LY231514 Pharmacokinetic Parameters (Day 1)

Parameter	Arithmetic Mean (CV as %) Dose (mg/m²)									
	0.2 (n=2)[a]	0.4 (n=4)	0.52 (n=2)[a]	0.78 (n=2)[a]	1.2 (n=2)[a]	1.8 (n=4)	2.3 (n=2)[a]	3 (n=3)	4 (n=4)	5.2 (n=1)
C_{max} (ng/mL)	29.8 – 32.7	68.8 (36%)	73.9 – 111	129 – 168	92.5 – 143	291 (29%)	44.9 – 397	544 (59%)	734 (18%)	937
$AUC_{0-\infty}$ (ng•hr/mL)	22.6 – 37.8	42.8 (28%)	77.9 – 78.9	91.9 – 139	59.9 – 72.9	215 (40%)	66.5 – 353	700 (50%)	561 (32%)	693
T_{max} (hr)[a]	0.08	0.08	0.08 – 0.25	0.08	0.08	0.08	0.08 – 0.25	0.08 – 0.5	0.08	0.08
CL_p (mL/min)	176 – 251	261 (32%)	188 – 203	150 – 236	439 – 501	262 (41%)	208 – 1052	163 (75%)	247 (35%)	179
CL_p (mL/min/m²)	90.3 - 148	166 (28%)	110 – 111	93.6 – 143	274 – 339	158 (39%)	108 – 572	93.1 (70%)	131 (42%)	125
V_{ss} (L)	10.5 – 14.3	12.8 (43%)	8.41 – 28.3	10.1 – 14.8	19.6 – 28.2	13.9 (19%)	16.0 – 121	18.2 (75%)	15.1 (25%)	11.5
V_{ss} (L/m2)	6.18 – 7.32	8.04 (32%)	4.95 – 15.3	6.14 – 9.26	12.3 – 19.1	8.44 (19%)	8.31 – 65.5	10.4 (70%)	8.01 (29%)	8.06
$t_{1/2}$[b] (hr)	0.5 – 1.0	0.7	0.7 - 1.9	0.6 – 1.4	0.7 – 0.9	0.8	1.0 - 1.4	1.6	1.0	1.0

[a] both values are reported when n=2

[b] harmonic mean

Table BP00.5. Summary of Mean Pharmacokinetic Parameters by Gender and Day of Administration

Parameter	Arithmetic Mean (CV as %)			
	Males		Females	
	Day 1	Day 5	Day 1	Day 5
C_{max}[a] (ng/mL)	342 (37%)	485 (49%)	422 (34%)	388 (31%)
$AUC_{0-\infty}$[a] (ng•hr/mL)	289 (40%)	342 (53%)	338 (54%)	445 (59%)
CL_p (mL/min)	305 (81%)	236 (43%)	249 (48%)	224 (76%)
CL_p (mL/min/m²)	167 (80%)	137 (51%)	158 (52%)	142 (76%)
V_{ss} (L/hr)	25.4 (120%)	13.7 (30%)	14.3 (54%)	15.4 (23%)
V_{ss} (L/hr/m²)	13.9 (119%)	7.87 (34%)	8.93 (52%)	9.63 (22%)

[a] Values normalized to a 4 mg dose

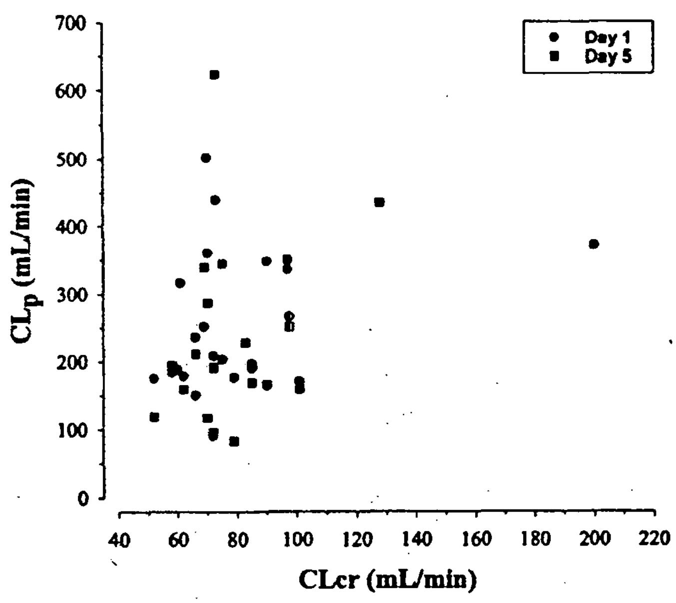


Figure BP00.3 Relationship between CL_p and measured creatinine clearance (CL_{cr}).

Table BP00.4. Results of Dose Proportionality Analysis

Parameter	β	p-Value for Hypothesis "β=1"	Conclusion
C_{max}		—	Dose proportional
$AUC_{0-\infty}$	1.06	0.280	Dose proportional

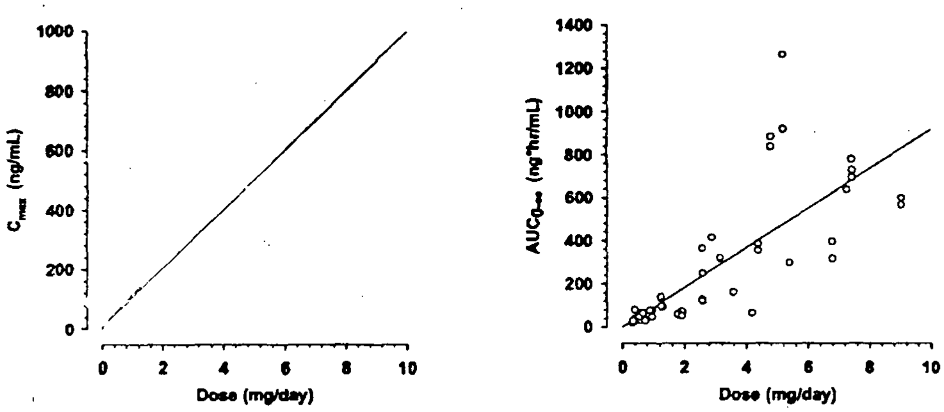


Figure H3E-BP00.2. Relationship between C_{max}, $AUC_{0-\infty}$ and dose.

Includes data from Day 1 and 5

Sponsor conclusions
AUC and Cmax dose-proportional from 0.2 to 5.2 mg/m2
MTA not dependent upon sex or administration day
No apparent accumulation over 5 days
No relationship between Cl and CLcr

Comments
Assay may be problematic
Lack of CLcr relationship needs explanation
Some prolonged exposure; maybe limited by analytical method; longer t1/2; some high concentrations need explanation: biliary recirculation?

ADME Report 15
From study JMAW

Urine from 4 patients was used to attempt to identify two metabolites observed in urine samples from animals. These metabolites were LY338979 (M1) and LY368962 (M3). Only parent and M1 were detected.

JMCH MTA plus cisplatin in malignant mesothelioma

Phase 3, no prior chemo, malignant pleural mesothelioma
Objectives
1. effect of cisplatin on LY231514 PK
2. effect of folic acid and vitB12 on LY213514 PK
3. identify pop pk model for cisplatin and estimate cl
4. investigate LY231514 on total platinum clearance.

RX 1: MTA 500 mg/m2 iv for 10 minutes, then cisplatin 75 mg/m2 over 2 hrs, beginning 30 minutes post MTA.

RX 2: saline iv for 10 min, then 75 mg/m2 cisplatin over 2 hours, beginning 30 min post MTA.

Regimen: Day 1 administration once every 21 days.
Formulation: aqueous solution.

Supplement: Both arms to receive oral folic acid 350-600 ug/day and B12 1000 ug i.m. every 9 weeks, 1 to 3 weeks prior to study drug.

JMAP 15 patients: 2-arms a: MTA + cisplatin on same day, b: MTA day 1 and cisplatin day 2. No difference in PK.

Biaonalytical: LC/MS/MS —— ng/ml for MTA
Cisplatin (II) atomic absorption 50 to 1999 ngPt/ml and 50 to 2008 ngPt/ml MDS
Sampling: 1 to 4 samples per plasma concentration. Sampling during cycles 1 and 3
MTA: 9.5 min, 2 h40 min, 4-8 hr, 20-28 hr, 44-53 hr. Last sample later deleted from analysis

BSA: $(kg)^{0.425}$x $(cm)^{0.725}$x71.84/10000= m2
CGCL=(140-age)xkg/(72xserumcreatinine)---male
CGCL=(140-age)xkg/(72xserumcreatinine)x0.85---female
When were CLcr determined?

Handling Outliers

1. Post-infusion concentrations that increased by at least 25% relative to the previous time-point.
2. Datapoints that were obviously mislabeled; datapoints with obvious 24- hour shift (misdated) or 12-hour shift (use of 12-hour clock time instead of 24-hour clock time).

3. Five observations in the total platinum dataset and 10 observations in the L Y231514 dataset were identified as potential outliers during visual inspection of the respective composite concentration-time plots and subsequently eliminated from the dataset as statistically implausible (that is, greater than 3 standard deviations from the mean log-transformed concentrations for the corresponding time points).
4. Because data excluded under categories 1 through 3 may indicate sample handling issues applicable to all observations in the cycle, the entire plasma concentration-versus time profile was excluded from analysis .
The data excluded from analysis were categorized as "primarily unevaluable" (for example, categories 1 through 3) or "secondarily unevaluable" (category 4 above). JMCH LY231514 Datasets 1 and 2, and the total platinum dataset were prepared by removing both primarily and secondarily unevaluable data."

Modeling
Used pop PK model; 2-C proportional error on inter-patient variability and residual error. Creatinine clearance on CL and BSA on V were incorporated into this model. Due to over parameterization, developed model for current study only. Model was simplified. FOCE/I used BSA appears to have been eliminated.

$TVCL=(\theta1 + \theta5xCGCL/107.4)$, where $\theta1$ intercept, $\theta5$ slope of CL vs CGCL, 107.4 is median CGCL from study,

Effect of cisplatin on MTA by dichotomous variable on CL, V1 and V2 individually, and accepted based on MOF. Effect of folic acid (FA) and VitB12 (VB12) was assessed by dichotomous variable on CL. FA on admin day, FA 5days prior to admin day, VB12 on admin day and VB12 5 days prior to admin day tested.

$TVCL=(\theta1 + \theta5xCGCL/92.6)$,

$TVV1= (\theta2xBSA^{\theta6})x[(1-I1)+(\theta7xI1)]$

$TVV2= \theta4x[(1-I1)+(\theta7xI1)]$

where $\theta1$ intercept, $\theta5$ slope of CL vs CGCL,

$\theta2$ and $\theta6$ are the leading coefficent and exponent of the relationship between V1 and SA as quantified by a power function.

$\theta7$ is the magnitude of the effect of cisplatin coadministration on each f the model parameters

$I1$ is an indicator variable that is 0 MTA as single agent, and 1 for MTA + cisplatin.

Cisplatin

Total platinum modeled with 2-C (CL, V1, V2 and Q). IIV and residual variability modeled by proportional error, used FOCE/I. Parameter sensitivity and leverage done to ensure global minimization.. Effect of MTA determined by adding dichotomous variable to pt CL.

$P=\theta1[(1-I1)+(\theta2I1)]$

Sensitivity. Set parameter to population mean and adding of 120%. NONMEM estimated all other parameters monitor MOF

Leverage: 10 subsets of index set. Used final model. Compared leverage parameters to full model parameters; anything falling outside the 95%CI for parameter indicates subset of patients with undue influence. Then reversed. Used parameters of subsets on all study/index data to see if there was a difference.
Results

Excluded 32 36 hr timepoints from dataset.

Table JMCH.5. Summary of Baseline Age, Body Surface Area, Weight and Cockcroft-Gault Creatinine Clearance for JMCH Study Patients and Patients in the Reference Dataset

	Age [a] (years)	BSA [a] (m^2)	Weight [a] (kg)	CGCL [a] (mL/min)
Reference Dataset (n=209)				
Range	26.3 – 79.1	1.26 – 2.50	34.0 - 138	44.3 – 225
Mean (CV as %)	57.3 (19)	1.76 (14)	68.3 (25)	96.9 (32)
JMCH LY231514 Datasets 1 and 2 (n=70)				
Range	38.09 – 85.61	1.5988 – 2.2137	54.8 – 111.1	53.564 – 232.352
Mean (CV as %)	63.9 (14)	1.93 (7.62)	78.5 (14.2)	109.5 (28.9)
JMCH Cisplatin Dataset (n=140)				
Range	38.09 – 85.61	1.5823 – 2.4938	55.3 – 140.3	53.564 – 232.352
Mean (CV as %)	64.6 (13.7)	1.96 (8.63)	81.2 (16.1)	110 (30.6)

Abbreviations: BSA = Body Surface Area, CGCL = Cockcroft-Gault creatinine clearance.
[a] Baseline patient characteristics.

Table JMCH.6. **Gender, Smoking and Alcohol Consumption Status of JMCH Study Patients and Patients in the Reference Dataset**

	Gender (% total patients [a])		Smoking Status (% total patients [b])		Alcohol (% total patients [c])	
	Male	Female	Yes	No	Yes	No
Reference Dataset (n=209)	51.7	48.3	31.1	68.9	23.9	73.2
JMCH LY231514 Datasets 1 and 2 (n=70)	87.1	11.4	8.57	87.1	44.3	47.1
JMCH Cisplatin Dataset (n=140)	88.6	10.7	10.7	87.1	45.7	49.3

[a] Data missing for 1 patient (1.43%) in JMCH LY231514 Datasets 1 and 2 and 1 patient (0.71%) in JMCH Cisplatin Dataset.

[b] Data missing for 3 patients (4.29%) in JMCH LY231514 Datasets 1 and 2, and 3 patients (2.1%) in JMCH Cisplatin Dataset.

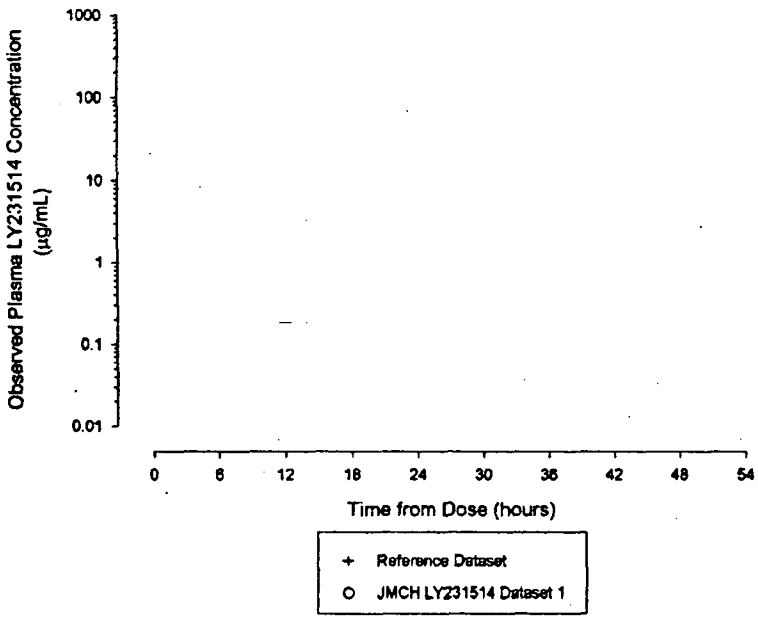
[c] Data missing for 6 (2.9%) patients in the reference dataset, 6 patients (8.57%) in JMCH LY231514 Datasets 1 and 2, and 7 patients (5.0%) in JMCH Cisplatin Dataset.

Table JMCH.7. **Summary of Ethnic Origin for JMCH Study Patients and Patients in the Reference Dataset**

Ethnic Group	Reference Dataset	JMCH LY231514 Datasets 1 and 2	JMCH Cisplatin Dataset
Caucasian	160 (77%)	66 (94.3%)	135 (96.4%)
African Descent	35 (17%)	1 (1.43%)	1 (0.714%)
Asian	2 (1%)	0	0
Hispanic	2 (1%)	2 (2.86%)	3 (2.14%)
Other [a]	10 (5%)	1 (1.43%)	1 (0.714%)
N [b]	209	70	140

[a] Undefined ethnic origin.

[b] N = total number of patients included in the pharmacokinetic analyses.



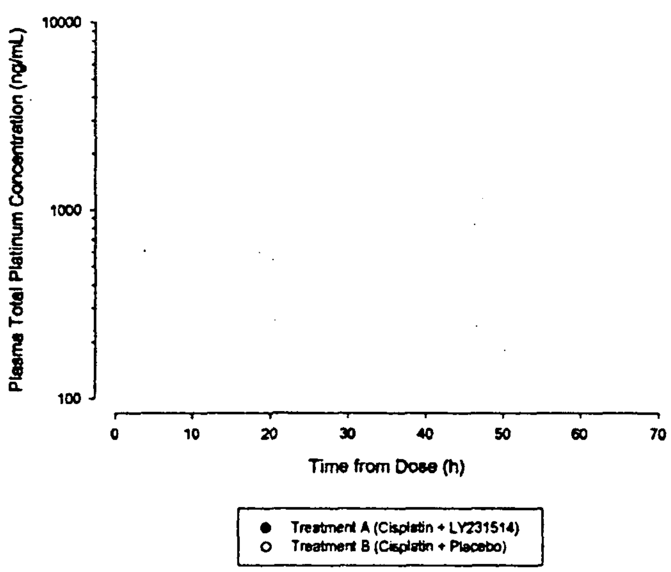


Figure JMCH.10. **Observed Plasma Total Platinum Concentrations versus Time from Start of Infusion (all doses)**

PopPK estimates for JMCH and reference dataset using previous (original model) model.

Table JMCH.9. Population LY231514 Pharmacokinetic Parameter Estimates (%SEE)

Parameter Description	Reference Dataset	JMCH LY231514 Dataset 1	JMCH LY231514 Dataset 2
Clearance			
TVCL, base parameter for CL (mL/min)	43.0 (16.6)	18.0 (71.6)	58.3 (25.3)
Θ_1, parameter for effect of CGCL on CL (mL/min)	47.2 (14.8)	59.0 (20.3)	28.7 (41.0)
CL (mL/min)=TVCL + Θ_1•CGCL/92.6	90.2	86.4[a]	91.6[a]
Interpatient variability	19.3% (14.1)	26.4% (25.8)	17.1% (35.7)
Central Volume of Distribution			
TVV1, base parameter for V_1 (L)	6.13 (9.04)	5.58 (29.0)	4.92 (33.3)
Θ_2, parameter for effect of BSA on V_1	1.32 (11.6)	0.892 (49.7)	0.877 (58.8)
V_1 (L)=TVV_1•$BSA^{\Theta 2}$	12.7	10.1[b]	8.80[b]
Interpatient variability	16.6% (29.3)	14.7% (47.0)	16.2% (92.4)
Intercompartmental Clearance			
Parameter for Q (mL/min)	14.5 (17.6)	3.5 (20.4)	76 (49.3)
Interpatient variability	NE	NE	NE
Peripheral Volume of Distribution			
Parameter for V_2 (L)	3.38 (10.9)	1.93 (13.4)	7.82 (21.1)
Interpatient variability	24.5% (24.6)	36.6% (33.2)	14.2% (127)
Residual Error (proportional)	28.4% (8.20)	35.1% (11.6)	30.4% (15.5)

Abbreviations: NE = Not estimated, SEE = Standard error of the estimate.

[a] Median CGCL for JMCH LY231514 Datasets 1 and 2 = 107.4 mL/min.

[b] Median BSA for JMCH LY231514 Datasets 1 and 2 = 1.94 m^2.

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CL of MTA in these patients similar to refence data (86, 82 vs 90 ml/min. V1 and V2 are lower. This indicates overparamterization. Therefore, simplified PPK model

Summary Table 2. Study JMCH LY231514 Pharmacokinetic Parameter Estimates (%SEE)

Parameter Description	JMCH LY231514 Dataset 1		JMCH LY231514 Dataset 2	
	JMCH Base Model	JMCH-CGCL Model	JMCH Base Model	JMCH-CGCL Model
MOF	5183.937	5148.551	4843.383	4830.668
Clearance				
TVCL, base parameter for CL (mL/min)	80.8 (4.14)	18.2 (77.4)	102.8 (4.12)	57.7 (24.1)
Θ_1, parameter for effect of CGCL on CL (mL/min)	NE	64.7 (23.5)	NE	32.0 (37.8)
CL (mL/min)=TVCL + Θ_1•CGCL/107.4[a]	80.8	82.9	102.8	89.7
Interpatient variability	34.9% (20.0)	30.8% (24.4)	22.1% (17.9)	20.1% (19.7)
Central Volume of Distribution				
Parameter for V_1 (L)	10.0 (4.09)	9.90 (3.85)	6.40 (13.3)	8.17 (5.73)
Intercompartmental Clearance				
Parameter for Q (mL/min)	2.58 (17.4)	2.57 (16.4)	398.3 (34.4)	83.0 (55.8)
Peripheral Volume of Distribution				
Parameter for V_2 (L)	1.76 (14.3)	1.81 (14.1)	15.2 (11.7)	8.08 (26.6)
Residual Error (proportional)	42.3% (10.3)	41.1% (9.11)	32.2% (13.9)	33.0% (13.9)

Abbreviations: NE = Not estimated, SEE = Standard error of the estimate.
[a] Median CGCL for JMCH LY231514 Datasets 1 and 2 = 107.4 mL/min.

Dropping the 36 and onward timepoint was more consistent with the reference set of data Dataset2). Confirmed by SAS analysis (p=0.68 for dataset 2, 0.008 for dataset 1).

No effect of cisplatin on CL or V2 (δMOF of –0.52, -0.004), but did affect V1 (δMOF of –57.2). 30% reduction in parameter estimate. Expect Increased Cmax, no change in AUC, t1/2. No alteration in dosing needed.

FA and VB12 no effect on MTA CL (δMO of 0.001 to –0.96).

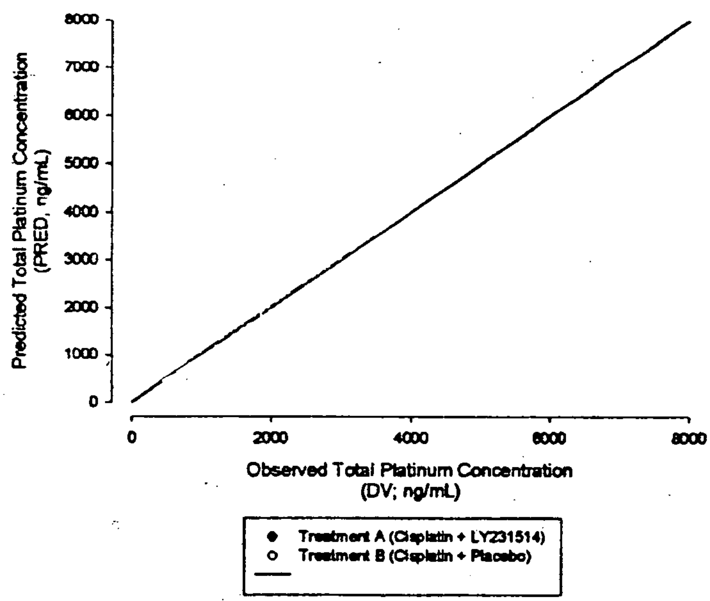
Cisplatin

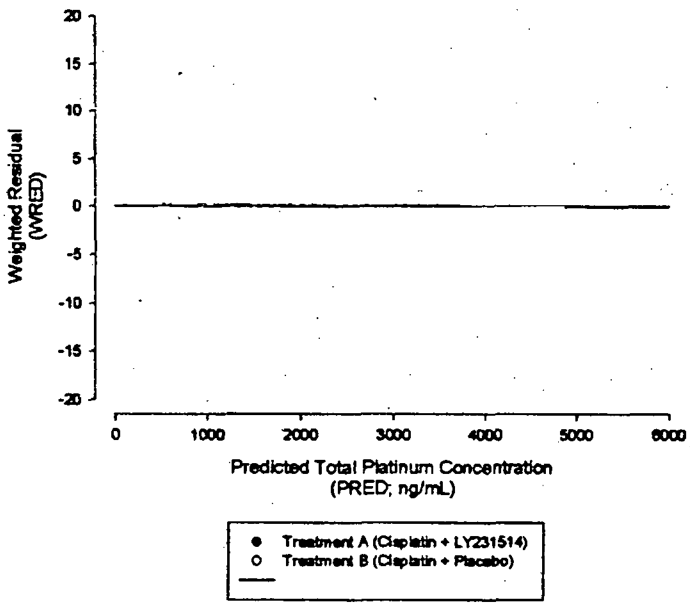
Summary Table 5. Pharmacokinetic Parameters of Cisplatin Using Population Pharmacokinetic Base Model

Parameter Description	Population Estimate (%SEE)	Interpatient Variability (%SEE)
Clearance		
Parameter for CL (mL/min)	12.3 (7.63)	41.5% (28.3)
Central Volume of Distribution		
Parameter for V_1 (L)	32.9 (7.75)	37.9% (20.4)
Intercompartmental Clearance		
Parameter for Q (mL/min)	312 (14.0)	—
Peripheral Volume of Distribution		
Parameter for V_2 (L)	52.0 (4.50)	—
Residual Error (proportional)	17.1% (10.2)	

Abbreviations: SEE = standard error of the estimate.
Method: FOCE with interaction.

Parameters similar to literature values. MTA had no effect on Pt CL (δMOF 0.506).





Parameter sensitivity

Model is acceptable because parameter sensitivity 95% CI wider than actual error measurements.

Table JMCH.15. Confidence Intervals (95%) for Cisplatin Population Pharmacokinetic Parameter Estimates

Parameter	Parameter Estimate	Calculated[a] 95% Confidence Interval Lower	Calculated[a] 95% Confidence Interval Upper	Parameter Sensitivity 95% Confidence Interval Lower	Parameter Sensitivity 95% Confidence Interval Upper
Base parameter for CL (mL/min)	12.3	10.5	14.1	10.18	14.19
Base parameter for V_1 (L)	32.9	27.9	37.9	28.73	36.53
Q (mL/min)	312	226	398	266.9	382.6
V_2 (L)	52.0	47.4	56.6	48.35	55.99
Interpatient Variability on CL	0.172	0.0765	0.267	0.0881	0.3005
Interpatient Variability on V_1	0.144	0.0864	0.202	0.1014	0.21
Residual Error	0.0293	0.0234	0.0352	0.02506	0.03463

Abbreviations: CL = clearance, V_1 = central volume of distribution, Q = intercompartmental clearance, V_2 = peripheral volume of distribution.

[a] Standard calculation for 95% confidence interval: Parameter Estimate ± 1.96*Std. Error of Estimate from NONMEM results.

Leverage analysis

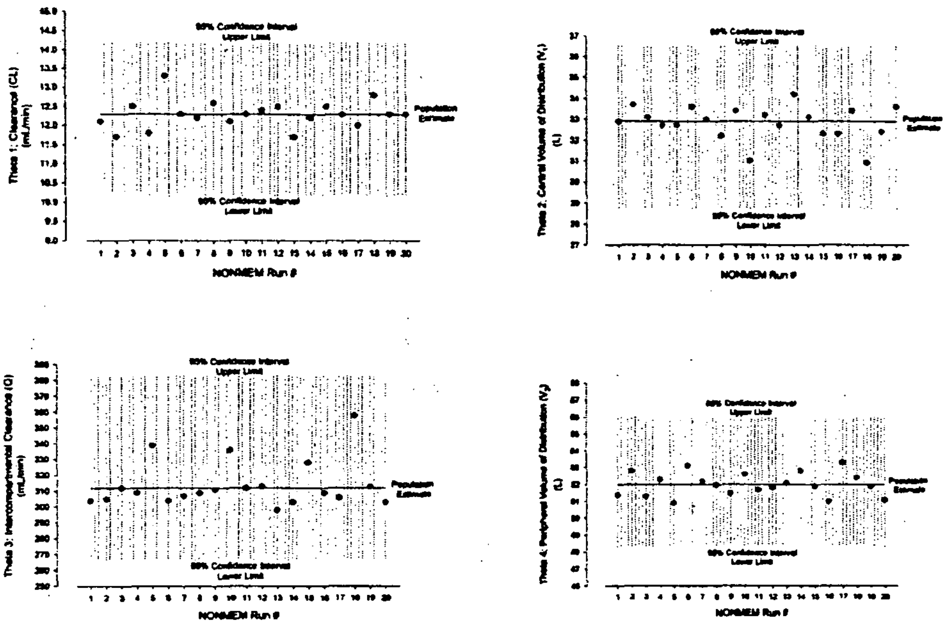


Figure JMCH.14. Pharmacokinetic Parameter Estimates Obtained From Leverage Analyses in Comparison with Base Model Parameter Estimates and 95% Confidence Intervals

No apparent differences due to subsets of patients

Concluded that the PPK model for cisplatin was accurate.
Incorporating MTA as a covariate on cisplatin generated delta MOF 0.506. Therefore, no effect of MTA on cisplatin clearance.

Conclusions No effect of cisplatin on mTA. V1 was reduced, but no change in AUC, t1/2 or CL
No effect of FA or VB12 ON Mta
ciplatin pk same as literature.
mta does not affect cisplatin pk.

JMAW
MTA once every 21 days in renal impairment

Mechanism
1. inhibits thymidylate synthase (TS)
also 2) DHFR, and GARFT (glycinamide ribonucleotide formyl transferase).

Enters cell by reduced folate carrier. Is then glutamated. Pentaglutamate is .60 x more potent than monoglutamate.
Primary route of excretion is renal (70-90% of unchanged drug).

Objectives
- determine effect of renal function
- determine if CGCL is as good as lean body mass (CLBM)
- determine effect of FA and VB12 on CLp

Table JMAW.1. **LY231514 Dose Escalation Scheme**

Treatment Group	GFR (mL/min)	Dose Level	Dose (mg/m²)	No. of Patients
1A	≥80	1	500	3 to 6
		2	600	3 to 6
1B	60 - 79	1	500	3 to 6
		2	600	3 to 6
2	40 - 59	1	400	3 to 6
		2	500	3 to 6
3A	30 - 39	1	250	3 to 6
		2	300	3 to 6
		3	400	3 to 6
3B	20 - 29	Closed to accrual until further notice		
4	<20	Closed to accrual until further notice		

normal: 1a, b
one patient enrolled in group 4 died due to drug-related toxicity.

Formulation: MTA/mannitol

Infusion: 10 min i.v. once every 21 days
Sampling: 13 plasma samples out to 72 hrs
Urine: 0-4, 4-8, 8-12, 12-24, 24-48, 48-72
Analytical: LC/MS/MS ng/ml

CGCL= (140-yrs)x(kg)/(72xserumcreatinine (mg/dL))----male
CGCL= 0.85x(140-yrs)x(kg)/(72xserumcreatinine (mg/dL))----female

Lean Body Mass
LBM=0.3281x(kg)+0.33929(cm)---males
LBM=0.29569x(kg)+0.41813(cm)---females

CLBM=(140-yrs)xLBM/(71x serum creatinine (mg/dL))
Analysis: noncompartmental pk WinNonLinver 3.1
Fe= Ae0-72/Dose
CLr=FexCLp

Regression: $\ln(y)= \alpha+\beta x \ln(RF)$

α is leading coefficient, β is power slope

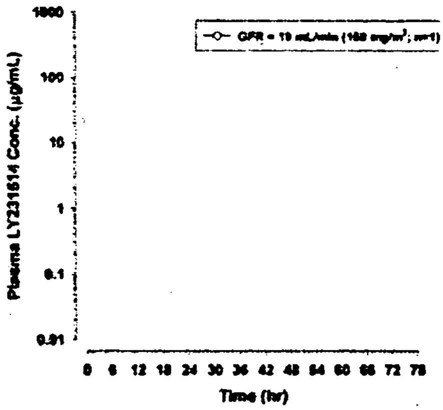
Table JMAW.2a. Summary of Administered Doses and Patient Demographics

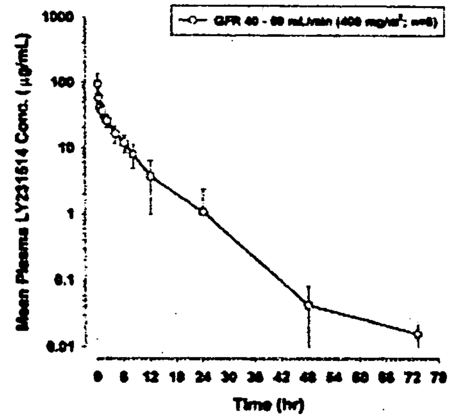
Group	Statistic	Dose (mg)	Age (yr)	Body Weight (kg)	BSA (m^2)
1A (n=18)	mean	1098	53.6	87.2	2.03
	SD	167	15.9	18.5	0.24
	min	840	25	61.6	1.63
	max	1368	76	123.8	2.48
1B (n=13)	mean	1029	62.6	82.2	1.91
	SD	209	10.6	21.5	0.25
	min	720	43	49.9	1.48
	max	1380	79	124.3	2.34
2 (n=15)	mean	827	65.3	71.7	1.80
	SD	153	10.0	17.7	0.22
	min	576	50	48.1	1.44
	max	1130	79	118.8	2.27
4 (n=1)	mean	304.5	79	84.8	2.04
	SD	NA	NA	NA	NA
	min	304.5	79	84.8	2.04
	max	304.5	79	84.8	2.04

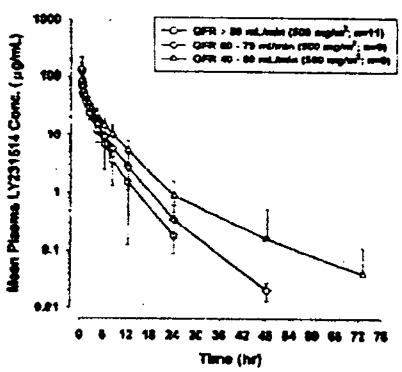
Table JMAW.2b. Summary of Patient Demographics

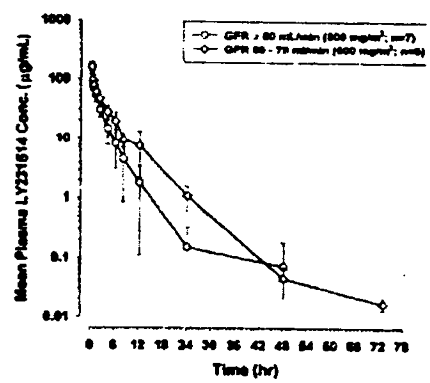
Group	Statistic	GFR (mL/min)	CGCL (mL/min)[a]	CLBM (mL/min)[a]	Gender Count
1A (n=18)	mean	112	116	79.8	
	SD	22.8	37.8	26.4	2 females
	min				16 males
	max				
1B (n=13)	mean	67.2	73.5	51.3	
	SD	4.81	14.1	12.4	4 females
	min				9 males
	max				
2 (n=15)	mean	50.8	54.6	40.7	
	SD	6.60	14.6	9.56	7 females
	min				8 males
	max				
4 (n=1)	mean	19	16.71	11.63	
	SD	NA	NA	NA	1 male
	min				
	max				

[a] n = 17 for CGCL and CLBM for Group 1A

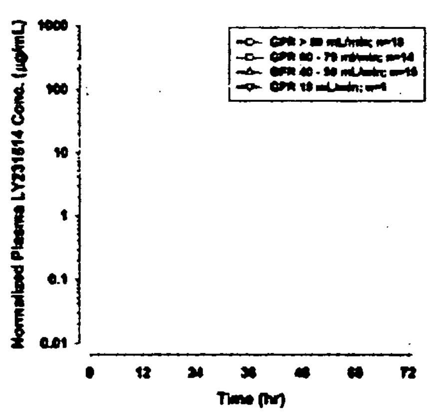








Plasma Concentration-Time Profiles
Normalized to a 900 mg Dose
(500 mg/m² x 1.8 m² BSA)



Urinary excretion. Cumulative amounts of excreted drug increased with renal function.
High variability.

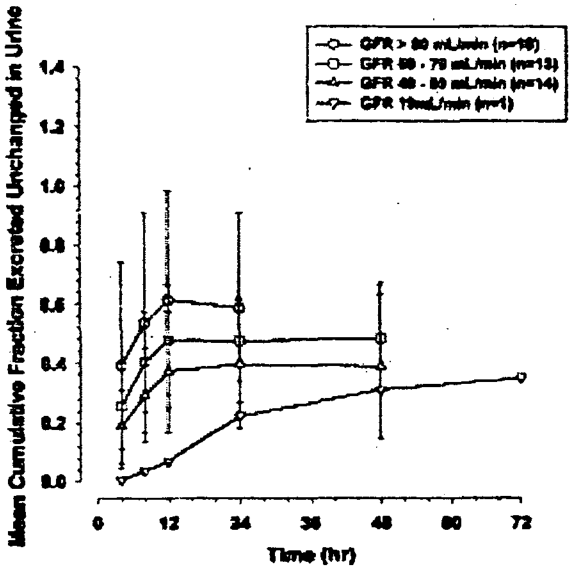


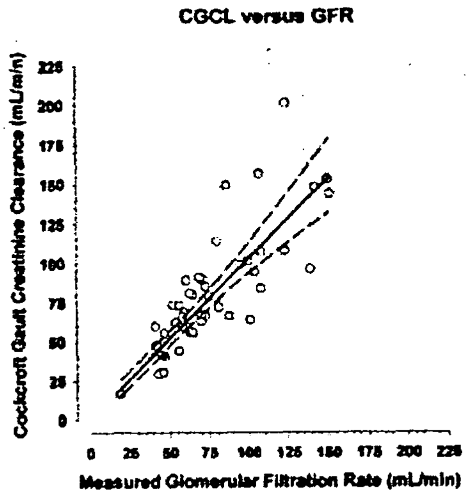
Table JMAW.3. Mean LY231514 Pharmacokinetic Parameters by Renal Function and Dose Groups

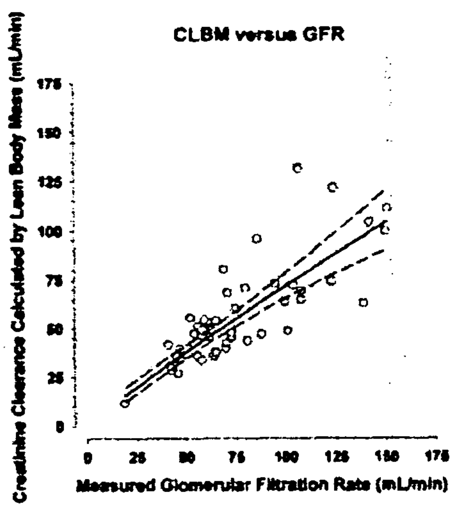
	Renal Function Groups						
	Group 1A (GFR ≥ 80)		Group 1B (60 ≤ GFR < 80)		Group 2 (40 ≤ GFR < 60)		Group 4 (GFR < 20 mL/min)
Parameter	500 mg/m² (n=11)	600 mg/m² (n=7)	500 mg/m² (n=8)	600 mg/m² (n=5)	400 mg/m² (n=6)	500 mg/m² (n=9)	150 mg/m² (n=1)
C_{max} (µg/mL)[a]	131 (29%)	153 (12%)	136 (54%)	138 (33%)	94.9 (40%)	91.4 (31%)	26.7
$AUC_{0-\infty}$ (µg•hr/mL)[a]	188 (27%)	228 (28%)	228 (27%)	373 (28%)	235 (36%)	300 (27%)	360
T_{max} (hr)[b]	0.15 (0.13 – 0.42)	0.15 (0.15 – 0.17)	0.15 (0.13 – 0.42)	0.15 (0.15 – 0.42)	0.17 (0.15 – 0.17)	0.15 (0.15 – 1.18)	0.17
CL_p (mL/min)[a]	93.2 (18%)	95.0 (25%)	69.6 (22%)	58.1 (22%)	54.4 (30%)	54.7 (34%)	14.1
CL_p (mL/min/m²)[a]	46.7 (21%)	47.2 (28%)	38.2 (22%)	28.1 (21%)	30.6 (27%)	29.7 (29%)	6.91
V_{ss} (L)[a]	20.2 (65%)	16.5 (27%)	16.6 (25%)	18.7 (32%)	17.1 (21%)	19.2 (35%)	26.6
V_{ss} (L/m²)[a]	9.75 (58%)	8.09 (24%)	8.99 (19%)	8.94 (24%)	9.69 (16%)	10.8 (44%)	13.1
$t_{1/2}$ (hr)[a]	4.4 (57%)	4.1 (39%)	5.0 (7.1%)	5.0 (9.7%)	5.3 (7.1%)	5.8 (46%)	19.4

[a] reported as arithmetic mean (%CV)

[b] reported as median (range)

CGCL,CLBM vs GFR





Both CGCL and CLBM provided linear relationships with GFR

Table JMAW.5. Statistical Analysis of CGCL and CLBM vs. GFR from Natural Logarithmically Transformed Data

Parameter	*Slope*	*95%CI*
CLBM: Creatinine using the LBM(mL/min)*	0.93	(0.75, 1.10)
CGCL: Creatinine clearance using CG(mL/min)**	0.99	(0.81, 1.16)

Abbreviations: CG = Standard Cockcroft Gault method; LBM = lean body mass formula.

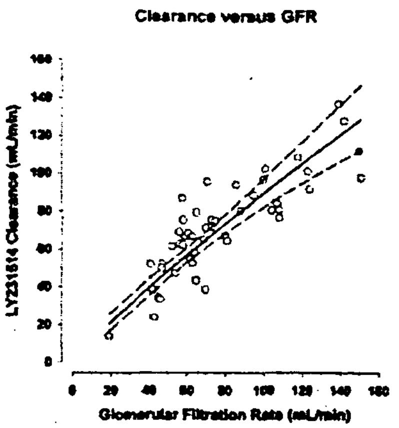
However, CLBM was negatively biased.

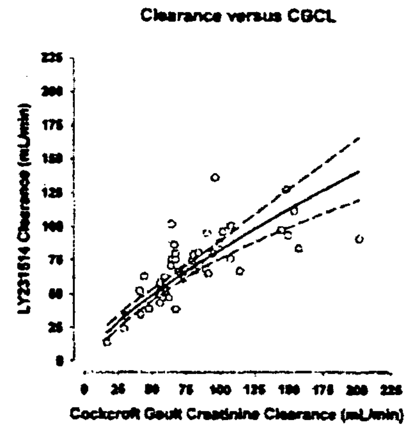
Table JMAW.6. Predicted CGCL and CLBM values for given GFR of 41mL/min with 95% CI

Parameter	*Predicted Value (mL/min)*	*95%CI*
CLBM: Creatinine using the LBM(mL/min)*	—	(27.9, 35.2)
CGCL: Creatinine clearance using CG(mL/min)**	—	(37.9, 48.2)

Abbreviations: CG = Standard Cockcroft Gault method; LBM = lean body mass formula.

Therefore, CGCL is considered more reliable in this case.





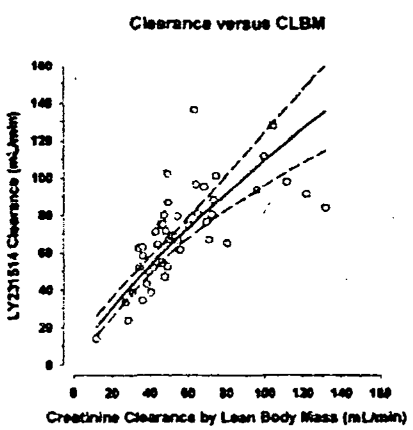


Table JMAW.7. Statistical Analysis of Plasma Clearance of LY231514 by Renal Function from Natural Logarithmically Transformed Data

Parameter	*Slope*	*95%CI*	*p_value*
CLBM: Creatinine using the LBM(mL/min)	0.7820	(0.6178, 0.9461)	0.0001
GFR: Glomerular filtration rate(mL/min)	0.8875	(0.7298, 1.0451)	0.0001
CGCL: Creatinine clearance using CG(mL/min)	0.7608	(0.6152, 0.9065)	0.0001

Abbreviations: CG = Standard Cockcroft Gault method; LBM = lean body mass formula.

Only GFR appears to give a truly accurate answer, as the other two methods have 95%CI that do not include 1.

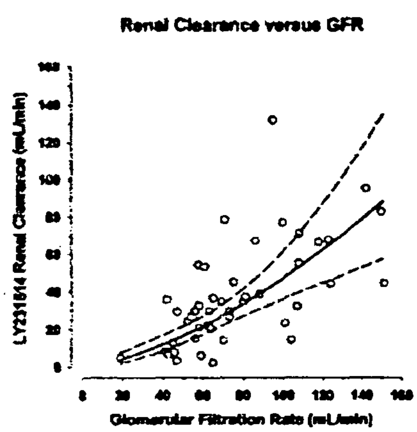
Table JMAW.8. **Statistical Analysis of Plasma Clearance of LY231514 by Renal Function and Patient Group from Natural Logarithmically Transformed Data**

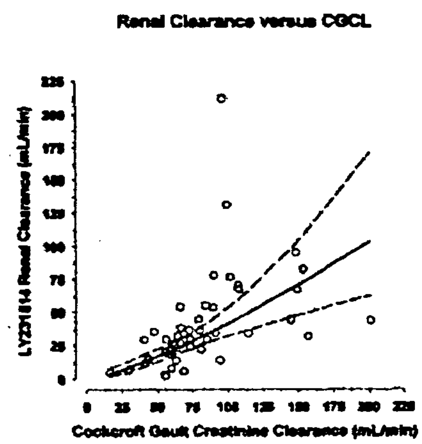
Normal Renal Function (Group 2; GFR > 80 mL/min)			
Parameter	*Slope*	*95%CI*	*p_value*
CLBM: Creatinine using the LBM(mL/min)	0.1793	(-0.1438, 0.5023)	0.2693
GFR: Glomerular filtration rate(mL/min)	0.7016	(0.1456, 1.2577)	0.0146
CGCL: Creatinine clearance using CG(mL/min)	0.1864	(-0.1195, 0.4924)	0.2258
Impaired Renal Function (Group 1; GFR ≤80 mL/min)			
Parameter	*Slope*	*95%CI*	*p_value*
CLBM: Creatinine using the LBM(mL/min)	0.9344	(0.7161, 1.1528)	< 0.0001
GFR: Glomerular filtration rate(mL/min)	1.1611	(0.8749, 1.4474)	< 0.0001
CGCL: Creatinine clearance using CG(mL/min)	0.8875	(0.6986, 1.0764)	< 0.0001

Abbreviations: CG = Standard Cockcroft Gault method; LBM = lean body mass formula.

The CGCL, CLBM does not hold for normal renal function.

Renal CL





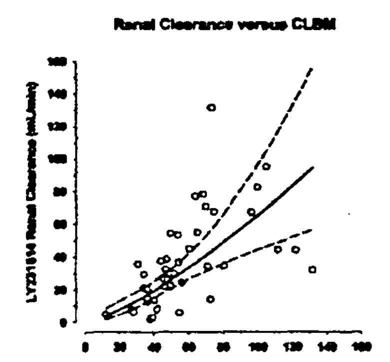


Table JMAW.9. Statistical Analysis of LY231514 Renal Clearance by Renal Function from Natural Logarithmically Transformed Data

Parameter	*Slope*	*95%CI*	*p_value*
CLBM: Creatinine using the LBM(mL/min)*	1.316	(0.8197, 1.8125)	0.0001
GFR: Glomerular filtration rate(mL/min)	1.516	(1.0136, 2.0175)	0.0001
CGCL: Creatinine clearance using CG(mL/min)**	1.301	(0.8470, 1.7544)	0.0001

Abbreviations: CG = Standard Cockcroft Gault method; LBM = lean body mass formula.

Table JMAW.10. Statistical Analysis of LY231514 Renal Clearance by Renal Function and Patient Group from Natural Logarithmically Transformed Data

Normal Renal Function (Group 2; GFR > 80 mL/min)			
Parameter	*Slope*	*95%CI*	*p_value*
CLBM: Creatinine using the LBM(mL/min)*	0.1801	(-0.8966, 1.2568)	0.7373
GFR: Glomerular filtration rate(mL/min)	1.1253	(-0.7450, 2.996)	0.2316
CGCL: Creatinine clearance using CG(mL/min)**	0.4004	(-0.6731, 1.4739)	0.4558
Impaired Renal Function (Group 1; GFR ≤80 mL/min)			
Parameter	*Slope*	*95%CI*	*p_value*
CLBM: Creatinine using the LBM(mL/min)*	1.3534	(0.6256, 2.0812)	0.0005
GFR: Glomerular filtration rate(mL/min)	1.5159	(0.5427, 2.4892)	0.0030
CGCL: Creatinine clearance using CG(mL/min)**	1.2649	(0.6009, 1.9289)	0.0004

Again, here, reanl function doesn't correlate with CLr in normal patients.

FA, VB12

No effect

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ON ORIGINAL

Table JMAW.11. Statistical Analysis of Vitamin Data: Effect of Concomitant Vitamin Administration on Plasma Clearance from Natural Logarithmically Transformed Data

Parameter	p_value	Comment
Folic acid being taken on the day of LY231514 administration	0.2444	No effect on CL
Folic acid in last 5 days prior to dose	0.0693	No effect on CL
Vitamin B12 being taken on the day of LY231514 administration	0.1688	No effect on CL
Vitamin B12 in last 5 days prior to dose	0.1733	No effect on CL

Table JMAW.12. Summary of Mean Predicted LY231514 Clearance and Renal Clearance Values over the Range of Measured Renal Function

Description	GFR (mL/min)	CGCL (mL/min)[b]	CL_p (mL/min)[a]	CL_r (mL/min)[a]	fu•GFR[c]	Ratio[e]
Severe Renal Impairment	19[c]	20.0	15.5	3.8	3.8	1.0
Moderate Renal Impairment	41	42.8	37.9	12.1	8.2	1.5
Mild Renal Impairment	60	62.2	59.0	21.5	12	1.8
Normal Renal Function[d]	80	82.7	82.4	33.3	16	2.1

[a] Predicted mean CL_p and CL_rv alues
[b] Predicted or calculated CGCL
[c] f_u, the fraction of drug unbound in plasma is approximately 0.2 (20%)
[d] lower limit of normal renal function
e ratio of predicted mean CL_r to fu•GFR.

Conclusions

- CLp, CLr correlated with GFR, CGCL, CLBM
- CLp, CLr improved with improving renal function
- No relationship witth normal renal function
- CGCL better than CLBM vs GFR
- Urine data highly variable
- Effective t1/2 3-6 hrs
- FA, BVB12 no effect on MTA CL
- Safety okay in mild, mod, normal. On epatient died in severe RI.

JMAW In Vitro Protein Binding ADME 14/21

Matrix: human plasma
Technique: ,
^{14}C-MTA (8.43 μCi/mg) concentrations: 451 to 4510 ng/ml 30 minutes at 37°C
liquid scintillation

Treatment Group	Glomerular Filtration Rate (GFR) (mL/minute)	Concentration (ng/mL)	Mean % Bound (SEM)	Range %
1A	≥80	4510	81.0 (0.8)[a]	74.6% - 85.9%
		451	82.0 (0.8)[a]	76.9% - 86.8%
1B	60-79	4510	81.8 (0.5)[a,d]	77.3% - 85.4%
		451	80.0 (0.6)[a,d]	76.4% - 84.1%
2	40-59	4510	79.4 (0.5)[b]	75.1% - 83.4%
		451	79.3 (0.8)[b]	74.9% - 85.4%
4	≤20	4510	76.9 (0.2)[c]	NC
		451	73.4 (1.4)[c]	NC

a = values obtained from 8 subjects in triplicate.
b = values obtained from 9 subjects in triplicate.
c = values obtained from a single subject in triplicate.
d = subject 5022 was analyzed twice.
NC = not calculated

Conclusion:

Protein binding was approximately 80% and unaffected by concentration or renal function. Similar to previous report (Wood P, 1995; Lilly ADME report 7).

Comment:

Check protein binding concentrations with in vivo plasma concentrations.

Addendum

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Table 1: **Mean Percentage of [^{14}C]LY231514 Bound to Plasma Proteins Following In Vitro Incubation in Human Plasma**

Concentration (µg/mL)	DPMs Plasma	DPMs Supernatant	% Bound	% Bound SEM
5		197	82.8	
		170	85.2	
		189	83.5	
Mean	1148	185	83.9	0.7
100		3624	82.8	
		3735	82.2	
		3621	82.8	
Mean	21033	3660	82.6	0.2
200		8179	80.0	
		7888	80.7	
		8092	80.2	
Mean	40903	8053	80.3	0.2

Therefore, plasma protein binding is approximately 80% and unaffected by concentration over the range of 0.5 to 200 ug/ml.

CYP 450 Interactions: ADME report 11 (Item 5 preclinical Pharmacology & Toxicology)

Objective: determine whether MTA inhibits human CYP 450 catalytic activity.
Human CYPs: 3A, 2D6, 2C9, 1A2

CYP 3A: midazolam (5 uM), microsomes (0.1 mg protein), 1mM NaDPH, 1 min incubation, 37°C. 1'-OH-midazolam monitored by HPLC (validated) MTA 354-885 uM

CYP 2D6: bufuralol (5 uM), microsomes (15 ug), 1 mM NaDPH, 30 min incubation, 37°C MTA 400 to 1000 uM. 1'-OH-bufuralol monitored by HPLC (validated).

CYP 2C9: diclofenac (2.5 uM), microsomes (50 ug), 1 mM NaDPH, 15 min incubation, 37°C MTA 400 to 1000 uM. 4'-OH-diclofenac monitored by HPLC (validated).

CYP 1A2: phenacetin (12.5 uM), microsomes (100 ug), 1 mM NaDPH, 30 min incubation, 37°C MTA 400 to 1000 uM. acetominophen monitored by HPLC (validated).

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Table 1: **Effect of LY231514 In Vitro on the CYP3A Mediated Metabolism of Midazolam to 1'-Hydroxy Midazolam**

Concentration of LY231514 (µM)	1'-Hydroxy Midazolam Formation (pmol/min/mg)	Percent of Control
0	950	100
354	818	86
531	786	83
708	847	89
885	752	79

Incubations contained microsomes, NADPH, and midazolam (5µM), with or without the addition of LY231514 as inhibitor (concentrations indicated above). All incubations were performed in duplicate with the average listed in the table.

Table 2: **Effect of LY231514 In Vitro on the CYP2D6 Mediated Metabolism of Bufuralol to 1'-Hydroxy Bufuralol**

Concentration of LY231514 (µM)	1'-Hydroxy Bufuralol Formation (pmol/min/mg)	Percent of Control
0	69	100
400	74	107
600	75	109
800	71	103
1000	73	106

Incubations contained microsomes, NADPH, and bufuralol (5 µM), with or without the addition of LY231514 as inhibitor (concentrations indicated above). All incubations were performed in duplicate with the average listed in the table.

Table 3: **Effect of LY231514 In Vitro on the CYP2C9 Mediated Metabolism of Diclofenac to 4'-Hydroxy Diclofenac**

Concentration of LY231514 (µM)	4'-Hydroxy Diclofenac Formation (pmol/min/mg)	Percent of Control
0	502	100
400	473	94
600	369	74
800	399	79
1000	466	93

Incubations contained microsomes, NADPH, and diclofenac (2.5 µM), with or without the addition of LY231514 as inhibitor (concentrations indicated above). All incubations were performed in duplicate with the average listed in the table.

Table 4: **Effect of LY231514 In Vitro on the CYP1A2 Mediated Metabolism of Phenacetin to Acetaminophen**

Concentration of LY231514 (µM)	Acetaminophen Formation (pmol/min/mg)	Percent of Control
0	204	100
400	190	93
600	192	94
800	178	87
1000	187	92

Incubations contained microsomes, NADPH, and phenacetin (12.5 µM), with or without the addition of LY231514 as inhibitor (concentrations indicated above). All incubations were performed in duplicate with the average listed in the table.

Conclusion

No significant interactions. Some inhibition of CYP 3A5, but at very high concentrations (885 uM)

Check:

Concentration in ng/ml against plasma concentrations

H3E-MC-JMAW(2b)
MTA + Aspirin

Based on prolonged t1/2 and toxicity in 3 patients. Possible mechanism-competitive inhibition of renal tubular secretion of methotrexate/MTA by salicylate. Maybe potein binding displacement.
Phase 1
Purpose: to determine effect of aspirin on the pharmacokinetics of MTA
N=24
Power of 80% to detect a 33% difference.
Dose: 500 mg/m2 alone, or 500 mg/m2 + enteric coated aspirin, crossed over
Regimen: 500 mg/m2 over 10 min every 21 days. (Cycle); Aspirin 625 mg enteric coated aspirin every 6 hrs 2 days prior to MTA. On day of study 325 mg aspirin administered 1 hr prior to MTA

Recruited patients with GFR >= 60 ml/min

Table JMAW.8.2. Blood Sampling Schedule for Plasma LY231514 Concentration Determinations

Sample Number	Sample Time
1	Immediately before dose
2	Immediately before the end of infusion (9.5 min)
3	15 minutes post-infusion
4	30 minutes post-infusion
5	1 hour post-infusion
6	2 hour post-infusion
7	4 hour post-infusion
8	6 hour post-infusion
9	8 hour post-infusion
10	12 hour post-infusion
11	24 hour post-infusion
12	48 hours post-infusion
13	72 hours post-infusion

Used Cockcroft-Gault

Table JMAW.9.1. Summary of Patient Demographic Data (n=24, Cycle 1)

	Age (yr)	Body Weight (kg)	Body Surface Area (m^2)	Creatinine Clearance[a] (mL/min)
Mean	53.4	71.8	1.84	119
SD	10.2	17.5	0.227	42.6
Minimum	34	47.5	1.4519	71.067
Maximum	70	123	2.3751	227.958

Abbreviation: SD = standard deviation
[a] Estimated from serum creatinine concentration using the Cockroft-Gault method (Cockcroft andGault 1976).

Simulated patient's plasma salicylate concentrations using dose/time data and following simulation parameters

Table JMAW.8.4 Enteric-coated Aspirin and Salicylate Pharmacokinetic Parameters Used in Simulations[a]

Parameter	Value
Absorption rate constant (K_a)	0.1694 hr^{-1}
Lag time of absorption (T_{lag})	7.9 ± 3.0 hr
Clearance	2.77 L/hr
Bioavailability (F)	0.62 ± 0.26
Elimination half-life ($t_{1/2}$)	4 hr
Elimination rate constant (K_{el})	0.1733 hr^{-1}
Volume of distribution	16 L
Time of maximum salicylate concentration (T_{max})	13.8 ± 4.5

[a] Mojaverian et al. 1987.

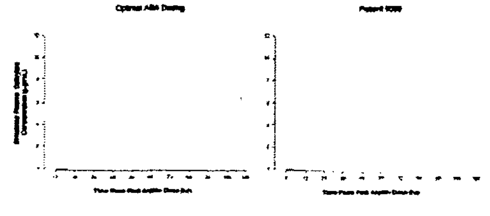

Figure JMAW.8.1. Simulated plasma salicylate concentration vs. time profile for optimal aspirin dosing and for a representative patient.

Table JMAW.9.1. Summary of Patient Demographic Data (n=24, Cycle 1)

	Age (yr)	Body Weight (kg)	Body Surface Area (m^2)	Creatinine Clearance[a] (mL/min)
Mean	53.4	78.8	1.84	110
SD	10.2	17.5	0.227	42.6
Minimum	34	47.5	1.4519	71.067
Maximum	76	123	2.3751	227.958

Abbreviation: SD = standard deviation

[a] Estimated from serum creatinine concentration using the Cockroft-Gault method (Cockroft and Gault 1976).

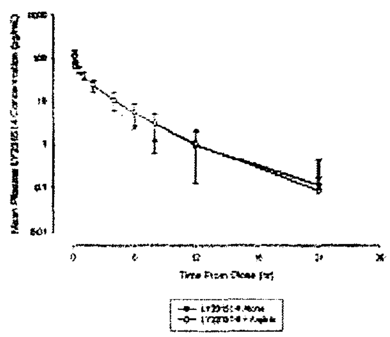

Figure JMAW.9.2. Graph of mean plasma LY231514 concentrations vs. time for LY231514 administered alone and in combination with aspirin.

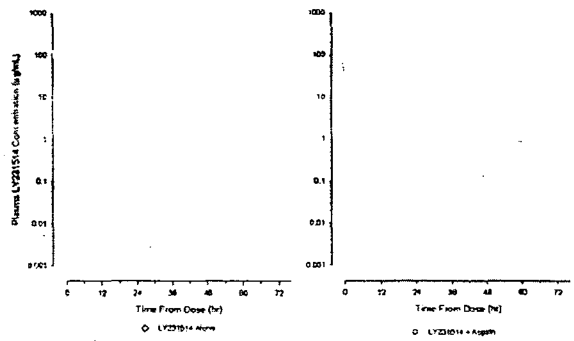

Figure JMAW.9.1. Observed plasma LY231514 concentrations vs. time for LY231514 administered alone and in combination with aspirin.

Table JMAW.9.2. Mean LY231514 Pharmacokinetic Parameters by Study Regimen[a]

Parameter	LY231514 Alone n=23[b]	LY231514 + Aspirin n=24
LY231514 Dose (mg)	923 (12.7%)	921 (12.3%)
LY231514 Dose (mg/m^2)	502 (0.764%)	500 (0.397%)
C_{max} (µg/mL)	114 (23.1%)	111 (28.6%)
Normalized C_{max}[d] (µg/mL/mg)	0.125 (31.3%)	0.124 (34.5%)
T_{max}[e] (hr)	0.15 (0.15 - 0.33)	0.15 (0.13 - 0.42)
$AUC_{0-\infty}$[f] (hr*µg/mL)	178 (33.1%)	170 (28.1%)
Normalized $AUC_{0-\infty}$[d,f] (hr*µg/mL/mg)	0.187 (35.7%)	0.189 (37.3%)
CL_p[f] (mL/min)	89.2 (32.5%)	98.1 (33.3%)
CL_p[c,f] (mL/min/m^2)	53.8 (29.2%)	52.8 (28.5%)
V_{ss} (L)	14.7 (23.7%)	15.9 (34.2%)
V_{ss}[c] (L/m^2)	7.97 (19.5%)	8.63 (32.7%)
$t_{1/2}$ (hr)	2.73 (31.9%)	2.85 (25.3%)

[a] Reported as Arithmetic Mean (CV%).
[b] Excluding data from Patient 5083.
[c] Normalized for body surface area.
[d] Normalized for absolute LY231514 dose.
[e] Reported as median (range).
[f] Predicted value. Observed value provided in Appendix JMAW.7 of this document.

Table JMAW.9.3. Least Square Geometric Mean Values for Each Treatment (LY231514+Aspirin/LY231514 Alone)

Parameter	Treatment regimen	Geometric Mean	95% CI	Ratio	95% CI
$AUC_{0-\infty}$ (hr*µg/mL)	Aspirin + LY231514	163.6	(146.0, 183.3)	1.00	(0.93, 1.08)
	LY231514 only	163.2	(145.6, 183.0)	.	.
Normalized $AUC_{0-\infty}$ (hr*µg/mL/mg)	Aspirin + LY231514	0.179	(0.157, 0.204)	1.00	(0.93, 1.08)
	LY231514 only	0.178	(0.156, 0.203)	.	.
C_{max} (µg/mL)	Aspirin + LY231514	107.5	(95.3, 121.2)	0.97	(0.87, 1.07)
	LY231514 only	111.3	(98.6, 125.7)	.	.
Normalized C_{max} (µg/mL/mg)	Aspirin + LY231514	0.118	(0.103, 0.135)	0.97	(0.87, 1.07)
	LY231514 only	0.122	(0.106, 0.140)	.	.
Clearance (mL/min)	Aspirin + LY231514	93.1	(81.7, 106.1)	1.00	(0.92, 1.07)
	LY231514 only	93.6	(82.1, 106.7)	.	.
Clearance (mL/min/m²)	Aspirin + LY231514	50.9	(45.5, 57.0)	0.99	(0.92, 1.07)
	LY231514 only	51.2	(45.7, 57.4)	.	.
$Volume_{ss}$ (L)	Aspirin + LY231514	15.1	(13.4, 17.1)	1.07	(0.97, 1.19)
	LY231514 only	14.1	(12.5, 16.0)	.	.
$Volume_{ss}$ (L/m²)	Aspirin + LY231514	8.28	(7.48, 9.18)	1.07	(0.97, 1.18)
	LY231514 only	7.75	(6.99, 8.60)	.	.

Abbreviations: CI = confidence interval.

Should there be such obvious differences in the mean Cmax and AUC, arithmatic vs geometric?

Table JMAW.10.1. LY231514 Pharmacokinetic Parameters, Studies JMAW2b Compared with JMAC, JMAD, JMAG, JMAH, JMAI, JMAJ, JMAK, and JMAM

	H3E-MC-JMAW		Eight Phase 2 Trials
Parameter	LY231514 Alone n=23	LY231514 + Aspirin n=24	LY231514 Alone n=209
CL_p (mL/min)	99.2 (32.5%)	98.1 (33.3%)	90.2
V_{ss} (L)	14.7 (23.7%)	15.9 (34.2%)	16.3

Sponsor Conclusion:

No need for dose adjust at this level of aspirin (1.3 gm/day)
Does not rule out interaction at higher doses (such as 2.5 to 3.9 gm/day)
CHECK GFR OF PATIENTS
STAT COMPARISON OF AUC0-24, BUT DATA OUT TO 72 HRS

H3E-MC-JMAW(1c)
MTA vs MTA + ibuprofen

Phase 1 Study
2 patients in JMAS were treated with naproxen, experienced severe toxicity.
Drug: 500 mg/m2 MTA

Power was 80% to detect a 33% difference with 24 patients.

Determine the influence of ibuprofen on MT pharmacokinetics.

Randomized crossover study. Patients with GFR >= 60 ml/min used.

MTA: 500 mg/m2 infused over 10 min once every 21 days.
Ibuprofen: 400 mg p.o. every 6 hrs 2 days prior to study day. Then 400 mg 1 hour priro to MTA

Table JMAW.8.2. **Blood Sampling Schedule for Plasma LY231514 Concentration Determinations**

Sample Number	Sample Time
1	Immediately before dose
2	Immediately before the end of infusion (~9.5 min)
3	15 minutes post infusion
4	30 minutes post infusion
5	1 hour post infusion
6	2 hour post infusion
7	4 hour post infusion
8	6 hour post infusion
9	8 hour post infusion
10	12 hour post infusion
11	24 hour post infusion
12	48 hours post infusion
13	72 hours post infusion

Same methods as aspirin;

Cockcroft-Gault used to calculate CLcr.

Simulated patient ibuprofen concentrations based on dose and time data and literature

Table JMAW.8.4. **Ibuprofen Pharmacokinetic Parameters Used in Simulations[a]**

Parameter	Value
Absorption rate constant (K_a)	0.6933 hr^{-1}
Clearance/F	3.84 L/hr
Elimination half-life ($t_{1/2}$)	2 hr
Elimination rate constant (K_d)	0.3465 hr^{-1}
Volume of distribution/F	11.5 L
Time of maximum ibuprofen concentration (T_{max})	2 hr

Abbreviation: F – bioavailability.
[a] (Davies 1998).

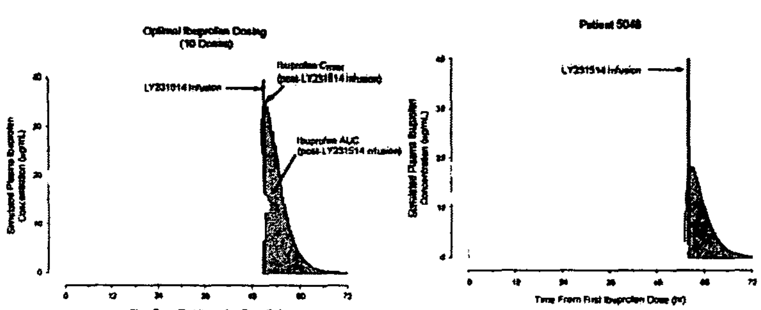

Figure JMAW.8.1. **Simulated plasma ibuprofen concentration vs. time profile for optimal ibuprofen dosing and for a representative patient.**

Table JMAW.9.1. Summary of Patient Demographic Data (N_{PK} = 24, Cycle 1)

	Age (yr)	Body Weight (kg)	Body Surface Area (m^2)	Creatinine Clearance[a] (mL/min)
Mean	60.8	76.2	1.89	115
SD	12.0	15.8	0.222	31.6
Minimum	35	49	1.4456	66.069
Maximum	80	100.2	2.2234	192.545

Abbreviation: SD = standard deviation

[a] Estimated from serum creatinine concentration using the Cockcroft-Gault method (Cockcroft and Gault 1976).

Assumed no change in CLcr. CHECK for change in CLcr in cycle 2.

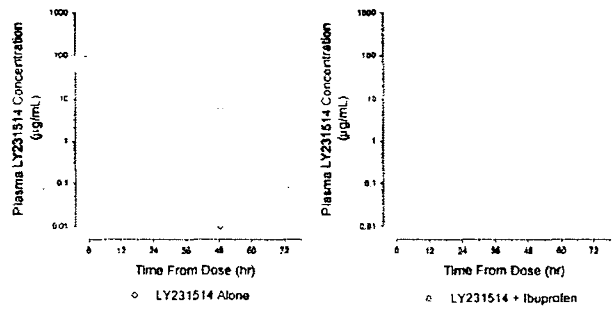

Figure JMAW.9.1. Observed plasma LY231514 concentrations vs. time for LY231514 administered alone and in combination with ibuprofen.

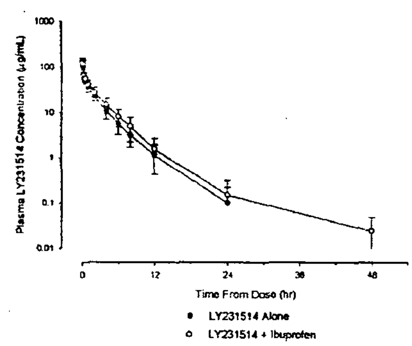

Figure JMAW.9.2. Graph of mean (± SD) plasma LY231514 concentrations vs. time for LY231514 administered alone and in combination with ibuprofen.

COMPARISON OF AUC0-24; CHECK AUC0-72

Table JMAW.9.3. Least Square Geometric Mean Values for Each Treatment (LY231514 + Ibuprofen/LY231514 Alone)

Parameter	Treatment regimen	Geometric Mean	95% CI	Ratio	95% CI
$AUC_{0-\infty}$ (hr*µg/mL)	Ibuprofen + LY231514	200.7	(182.1, 221.2)	1.22	(1.13, 1.33)
	LY231514 only	164.0	(148.7, 180.9)	.	
Normalized $AUC_{0-\infty}$ (hr*µg/mL/mg)	Ibuprofen + LY231514	0.214	(0.193, 0.237)	1.20	(1.12, 1.29)
	LY231514 only	0.178	(0.160, 0.197)	.	.
C_{max} (µg/mL)	Ibuprofen + LY231514	116.2	(102.7, 131.4)	1.16	(1.03, 1.30)
	LY231514 only	100.4	(88.6, 113.7)	.	
Normalized C_{max} (µg/mL/mg)	Ibuprofen + LY231514	0.124	(0.109, 0.141)	1.14	(1.03, 1.27)
	LY231514 only	0.109	(0.095, 0.123)	.	
CL (mL/min)	Ibuprofen + LY231514	78.0	(70.4, 86.3)	0.83	(0.78, 0.89)
	LY231514 only	93.8	(84.7, 103.9)	.	
CL (mL/min/m^2)	Ibuprofen + LY231514	41.5	(37.6, 45.7)	0.82	(0.77, 0.88)
	LY231514 only	50.3	(45.4, 55.5)	.	
V_{ss} (L)	Ibuprofen + LY231514	15.9	(14.3, 17.6)	0.93	(0.85, 1.02)
	LY231514 only	17.0	(15.3, 18.9)	.	
V_{ss} (L/m^2)	Ibuprofen + LY231514	8.44	(7.65, 9.32)	0.93	(0.84, 1.02)
	LY231514 only	9.11	(8.24, 10.08)	.	

Abbreviations: AUC (0-∞) = area under the concentration-time curve from the start of infusion through infinity; CI = confidence interval; CL = total systemic clearance; C_{max} = maximum observed plasma concentration; $t_{1/2}$ = half life; V_{ss} = volume of distribution at steady state.

Table JMAW.9.2. **Mean LY231514 Pharmacokinetic Parameters by Study Regimen[a]**

Parameter	LY231514 Alone N_{PK} = 23	LY231514 + Ibuprofen N_{PK} = 24
LY231514 Dose (mg)	932 (11.2%)	945 (11.4%)
LY231514 Dose[b] (mg/m²)	496 (4.41%)	500 (1.25%)
C_{max} (µg/mL)	105 (31.3%)	121 (27.9%)
Normalized C_{max}[c] (µg/mL/mg)	0.114 (34.4%)	0.129 (29.2%)
T_{max}[d] (hr)	0.15 (0.15 - 0.42)	0.15 (0.15 - 0.42)
$AUC_{0-\infty}$[e] (hr*µg/mL)	166 (23.6%)	208 (26.3%)
Normalized $AUC_{0-\infty}$[c,e] (hr*µg/mL/mg)	0.179 (21.0%)	0.220 (25.0%)
CL_p[e] (mL/min)	97.8 (24.0%)	80.4 (25.5%)
CL_p[b,e] (mL/min/m²)	52.5 (24.4%)	43.0 (27.2%)
V_{ss} (L)	17.6 (27.8%)	16.4 (26.9%)
V_{ss}[b] (L/m²)	9.34 (24.5%)	8.69 (26.2%)
$t_{1/2}$ (hr)	2.88 (19.5%)	2.88 (16.2%)

Abbreviations: AUC (0-∞) = are under the concentration-time curve from the start of infusion through infinity; CL_p = total plasma clearance; C_{max} = maximum observed plasma concentration; $t_{1/2}$ = half life; t_{max} = observed sampling time of C_{max}; V_{ss} = volume of distribution at steady state.

a Reported as Arithmetic Mean (CV%).

b Normalized for body surface area.

c Normalized for absolute LY231514 dose.

d Reported as median (range).

e Predicted value. Observed value provided in Appendix JMAW.7 of this document.

Sponsor's Conclusions

1.6gm/day decreased MTACL by 17; increased AUC by 20% and cmax by 15% P<0.05

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Appendix D. Pharmacometric review

Clinical Pharmacology and Biopharmaceutics

Pharmacometrics Review

NDA:	**21-462**
Volumes:	**9-15, item 6**
Compound:	**ALIMTA; MTA; pemetrexed**
Submission Date:	**10/24/2002**
Sponsor:	**Eli Lilly and Company**
Pharmacometrics Reviewers:	*Brian Booth*
	Roshni Ramchandani, Atul Bhattram
Pharmacometrics Team Leader:	**Joga Gobburu**
EDR submissions:	**See Appendix**

Title

Population Pharmacokinetic Analysis and PK/PD Correlations of Alimta

Overview

This review consists of three parts: the review of the applicant population pharmacokinetic modeling, the review of the applicant pharmacodynamic modeling of neutropenia, and FDA correlations of ALIMA dose and AUC to safety and effectiveness endpoints.

I. Applicant Population Pharmacokinetic Modeling of Alimta

Data

Model-Building

Data were obtained from 10 studies of ALIMTA in patients with varying types of cancer (see table x). Data were split into model-building (Index set; n=209) and model validation (Validation set; n=78) sets.

Study Data (JMCH)

The study data were derived from the pivotal clinical trial JMCH. Patients were treated with 500 mg/m^2 of Alimta over 10 minutes, which was followed 30 minutes later with a 75 mg/m^2 infusion of cisplatin over 2 hours. This treatment was repeated once every 21 days (1 cycle). Most of the patients were supplemented with folic acid/vitamin B12. Folic acid was administered as daily oral doses (350 to 600 μg)5 days prior to commencing Alimta. Vitamin B12 was administered intramuscularly (usually 1000 μg) once prior to treatment, and then once every three cycles.

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Table POPK.8.1. Studies Included in the Population Pharmacokinetic Analyses

Study Code	Cancer Type	LY231514 Doses and Duration of Infusion	Pharmacokinetic Blood Sampling Collection Intervals	Number of Patients Pharmacokinetic Assessment
Index Dataset:				
JMAC	Colorectal	324 to 1422 mg (150 to 684 mg/m²) 0.15 to 0.27 hours	0-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	15 F, 24 M
JMAD	Pancreatic	485 to 1494 mg (302 to 838 mg/m²) 0.13 to 0.25 hours	0-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	16 F, 19 M
JMAG	Breast	500 to 1260 mg (291 to 612 mg/m²) 0.17 to 0.25 hours	0-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	25 F
JMAH	Esophagus	650 to 1320 mg (448 to 639 mg/m²) 0.15 to 0.2 hours	0-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	4 F, 7 M
JMAI	Renal	960 to 1316 mg (563 to 631 mg/m²) 0.17 to 1.5 hours	0-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	6 F, 21 M
JMAJ	Head and Neck	555 to 990 mg (354 to 601 mg/m²) 0.05 to 0.33 hours	~9.5 minutes (end of infusion), 1-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	3 F, 23 M
JMAK	Bladder	562 to 1128 mg (374 to 613 mg/m²) 0.17 to 0.25 hours	~9.5 minutes (end of infusion), 1-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	14 M
JMAM	Cervical	470 to 1120 mg (338 to 617 mg/m²) 0.15 to 0.18 hours	0-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	32 F
Overall		324 to 1494 mg (150 to 838 mg/m²) 0.05 to 1.5 hours		101 F, 108 M
Validation Dataset:				
JMAL	Non small cell Lung	270 to 1320 mg (150 to 648 mg/m²) 0.15 to 0.35 hours	0-2 hrs, 2-6 hrs, 6-12 hrs, 12-36 hrs	19 F, 36 M
JMBR	Non small cell lung	244 to 1150 mg (126 to 510 mg/m²) 0.17 to 0.23 hours	~9.5 minutes (just prior to end of infusion), 1-4 hrs, 8-12 hrs	8 F, 15 M
Overall		244 to 1320 mg (126 to 648 mg/m²) 0.15 to 0.35 hours		27 F, 51 M

The demographic characteristics of the patients are listed in Table X.

Table 1. Demographic Characteristics of Patients in Studies (Model-Building sets)

Characteristic	Index set	Validation Set

	Mean (range)	Mean (range)
Gender	108 M, 101 F	51 M, 27 F
Age, years	57.3 (26 to 79)	60.6 (36.6 to 80)
Creatinine CL, ml/min	96.9 (44-223)	92.8 (40.7 to 112)
Body Weight, kg	68.3 (34 to 138)	69.3 (36 to 127)
BSA, m^2	1.76 (1.26 to 2.5)	1.78 (1.28 to 2.35)
Caucasian	160 (77 %)	59 (76 %)
African American	35 (17 %)	3 (4 %)
Asian	2 (1 %)	3 (4 %)
Hispanic	2 (1 %)	0
Other	10 (5 %)	13 (17 %)

Table 2. Demographic Characteristics of Patients in JMCH

Characteristic	Alimta (n=70)	Cisplatin (n=140)
	Mean (range)	Mean (range)
Gender	62 M, 98F	124 M, 16 F
Age, years	63.9 (38 to 85.6)	64.6 (38.1 to 85.6)
Creatinine CL, ml/min	109.5 (54-232.4)	110 (53.6 to 232.4)
Body Weight, kg	78.5 (54.8 to 111.1)	81.2 (55.3 to 140.3)
BSA, m^2	1.93 (1.59 to 2.21)	1.96 (1.58 to 2.49)
Caucasian	NA	NA
African American	NA	NA
Asian	NA	NA
Hispanic	NA	NA
Other	NA	NA

Once the model was built and validated, it was used to assess the pharmacokinetics of ALIMTA plus cisplatin the pivotal clinical trial, JMCH.

Methods

The plasma concentration-time course of ALIMTA was described by a two-compartment model with zero order input and first order elimination from the central compartment. This model was chosen based on previous analysis of data from phase 1 studies. A log-normal distribution was assumed for between-patient variability in CL, V1, Q and V2. First-Order (FO), first-order conditional (FOCE) and first-order conditional estimation with interaction (FOCE/I) methods were tested. Additive, proportional and combined error models were tested for the residual error. The final model chosen by the applicant was based on an examination of residual plots, correlation plots (e.g. predicted concentration vs. observed concentration), minimum objective function (MOF), and a sensitivity analysis. The effects of different covariates were investigated by sequentially adding covariates to model (see Table XX). Covariates were retained if the MOF decreased by 3.841 or more. Data from all doses were fit simultaneously with NONMEM (ver 5.0).

Table POPK.8.2. Patient Factors Assessed in the Population Pharmacokinetic Analysis

Continuous Variables	Categorical Variables
Age	Alcohol use
Alanine Transaminase (ALT)	Assay method (HPLC/LCMSMS)
Albumin	Ethnic origin
Alkaline Phosphatase	Folate Status (as assessed by Homocysteine, Methylmalonic Acid, Cystathionine, and Methylcitrate I and II)
Aspartate Transaminase (AST)	Gender
Body Mass Index	Smoking status
Body Surface Area	Treatment cycle (cycle = 1 versus cycle > 1)
Body Weight	
Creatinine Clearance (estimated by Cockcroft-Gault formula using age, weight, and serum creatinine)	
Creatinine Clearance (estimated by Cockcroft-Gault formula using age, lean body mass, and serum creatinine)	
Dose	
Serum Creatinine	
Total Bilirubin	
Total Protein	

Applicant's Results

CLcr caused a large reduction in MOF (95.065). Because this drug was extensively affected by CLCr, additional covaraitaes (which may have been confounded) were sequentially added to the model based on CLcr. The final model chosen by the applicant described CL as a function of the following covariates

$$TVCL = \theta_1 + \theta_5 \bullet (Clcr/92.6) \quad (1)$$
$$CL = TVCL \bullet \exp(\eta_1) \quad (2)$$

Where CL_{cr} is ml/min and 92.6 ml/min was the median Clcr in the study. Volume of distribution is described as

$$TVV = \theta_2 \bullet BSA^{1.32} \quad (3)$$
$$V = TVV \bullet \exp(\eta_2) \quad (4)$$

Final parameter estimates are listed in Table XX).

Table POPK.9.6. Pharmacokinetic and Covariate Parameters in Final Population Model for LY231514

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability (%SEE)
Clearance		
TVCL, base parameter for CL (mL/min)	43.0 (16.6)	19.3% (14.1)
Θ_1, parameter for effect of CGCL on CL (mL/min)[a]	47.2 (14.8)	
Central Volume of Distribution		
TVV1, base parameter for V_1 (L)	6.13 (9.04)	16.6% (29.3)
Θ_2, parameter for effect of BSA on V_1[b]	1.32 (11.6)	
Intercompartmental Clearance		
Parameter for Q (mL/min)	14.5 (17.6)	—
Peripheral Volume of Distribution		
Parameter for V_2 (L)	3.38 (10.9)	24.5% (24.6)
Residual Error (proportional)	28.4% (8.22)	

[a] $CL = TVCL - \Theta_1 \cdot CGCL/92.6$ where 92.6 is the median baseline CGCL.

[b] $V_1 = TVV1 \cdot BSA^{\Theta_2}$

Abbreviations: SEE = standard error of the estimate.

Method: FOCE with interaction

The goodness-of-fit of the final model is depicted in Figure 1, where the population plasma concentrations of Alimta are plotted against the observed concentrations from the study.

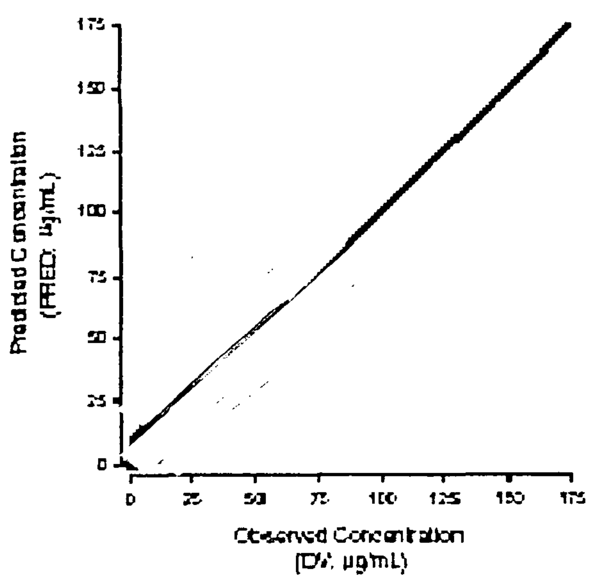

Figure 1: Population Predicted vs observed concentrations of Alimta; from Applicant

The predicted vs observed concentrations appear tightly clustered around the line of identity suggesting that the model satisfactorily fits the data. The tailing at higher concentrations of Alimta are observations derived predominantly from 6 patients. The applicant also demonstrated that the total clearance of ALIMTA is closely associated with CLcr (Figure X)

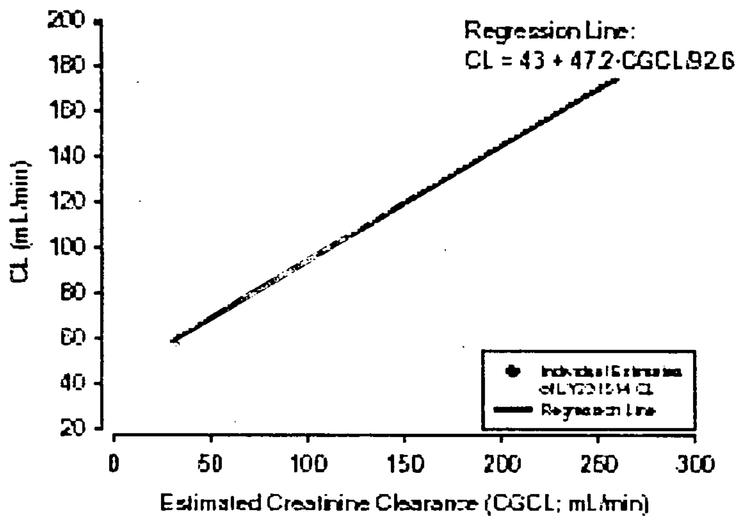

Figure 2. Relationship between CLcr and total systemic clearance of Alimta.

The sponsor validated the model using sensitivity and leverage analyses. The sensitivity analysis was performed by fixing a chosen parameter to the population estimate ± 5 to 40% and estimating the remaining parameters. The confidence intervals for these estimates were then determined. These data are listed in Table X

Table POPK.9.7. Confidence Intervals (95%) for LY231514 Population Pharmacokinetic Parameter Estimates (Index Dataset)

Parameter	Parameter Estimate	Calculated [a] 95% Confidence Interval Lower	Calculated [a] 95% Confidence Interval Upper	Parameter Sensitivity 95% Confidence Interval Lower	Parameter Sensitivity 95% Confidence Interval Upper
Base parameter for CL (mL/min)	43.0	29.0	57.0	34.9	51.0
Base parameter for V_1 (L)	6.13	5.04	7.22	5.14	7.34
Q (mL/min)	14.5	9.50	19.5	11.5	18.0
V_2 (L)	3.38	2.66	4.10	2.92	3.87
CGCL on CL	47.2	33.5	60.9	39.3	55.7
BSA on V_1	1.32	1.02	1.62	1.02	1.61
Between-Pt Var on CL	0.0374	0.0271	0.0477	0.0293	0.0478
Between-Pt Var on V_1	0.0277	0.0118	0.0436	0.0159	0.0441
Between-Pt Var on V_2	0.0602	0.0312	0.0892	0.0425	0.0848
Residual Error	0.0807	0.0677	0.0937	0.0729	0.0900

[a] Standard calculation for 95% confidence interval: Parameter Estimate ± 1.96 • Std. Error from NONMEM.

The applicant also conducted a leverage analysis using 10 leverage analysis datasets with 90% of the patients comparison of the confidence intervals for population estimates and differences in MOF indicated if any subgroup of patients had an undue influence on the final model chosen. The results of this analysis are listed in Table X.

Table POPK.9.8. - Range of Pharmacokinetic Parameter Estimates Obtained From Leverage Analyses in Comparison to Parameter Estimates and 95% Confidence Intervals (Index Dataset)

		Parameter Sensitivity 95% Conf Interval		Leverage Anlaysis Range of Values	
Parameter	Estimate	Lower	Upper	Analysis I	Analysis II
Base parameter for CL (mL/min)	43.0	34.9	51.0	37.8 - 47.2	40.5 - 45.2
Base parameter for V_1 (L)	6.13	5.14	7.34	5.70 - 6.40	5.86 - 6.51
Q (mL/min)	14.5	11.5	18.0	12.7 - 16.0	13.0 - 15.8
V_2 (L)	3.38	2.92	3.87	3.15 - 3.56	3.17 - 3.54
CGCL on CL	47.2	39.3	55.7	44.3 - 53.0	45.5 - 49.5
BSA on V_1	1.32	1.02	1.61	1.22 - 1.47	1.22 - 1.42
Between-Pt Var on CL	0.0374	0.0293	0.0478	0.0340 - 0.0406	0.0318 - 0.0396
Between-Pt Var on V_1	0.0277	0.0159	0.0441	0.0237 - 0.0323	0.0223 - 0.0310
Between-Pt Var on V_2	0.0602	0.0425	0.0848	0.0510 - 0.0681	0.0534 - 0.0645
Residual Error	0.0807	0.0729	0.0900	0.0775 - 0.0830	0.0753 - 0.0836

Abbreviations: CL = clearance; V_1 = central volume of distribution; Q = intercompartmental clearance;

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Phase 3 Trial: JMCH Alimta and cisplatin for the treatment of pleural mesothelioma.

The PPK model was used to assess the effects of cisplatin and folic acid/vitamin B12 supplementation on the pharmacokinetics of Alimta. A cisplatin PPK model was also developed to assess the effect of Alimta on total platinum pharmacokinetics.

From JMCH, 70 patients were available for PPK analysis following removal of unevaluable data points. Some of the patients in JMCH received Alimta and cisplatin. In order to provide a cisplatin-free comparator, these data were combined with the data from the patients used in the index set in the model building step described above. The final data set yielded 279 patients. The median value of CLcr in this dataset was 107.4 ml/min. Therefore, the PPK expression for clearance was altered, from 92.6 to

$$CL=\Theta_1 + \Theta_5 \bullet (CLcr/\mathbf{107.4}) \quad (3)$$

The effect of cisplatin was evaluated by adding cisplatin as a dichotomous variable.

$$CL=\Theta_1 + \Theta_5 \bullet (CLcr/\mathbf{92.6}) \bullet [(1-I1)+(\Theta_7 \bullet I1)] \quad (4)$$

Where $I1$ is an indicator variable where a value of 0 indicates Alimta alone and a value of 1 indicates cisplatin co-administration. A change in MOF of ≥ 3.841 were considered statistically significant. The effect of folic acid/vitamin B12 were determined in a similar fashion. A similar sub-model was used to evaluate the influence of cisplatin on volume of distribution of Alimta in the central compartment

A cisplatin PPK model was also developed to assess the effect of Alimta on cisplatin pharmacokinetics. The plasma concentration-time course of cisplatin was described by a two-compartment model with zero order input and first order elimination from the central compartment, based on previously published scientific literature describing cisplatin pharmacokinetics as either bi- or triphasic. A log-normal distribution was assumed for between-patient variability in CL, V1, Q and V2. First-Order (FO), first-order conditional (FOCE) and first-order conditional estimation with interaction (FOCE/I) methods were tested. Additive, proportional and combined error models were tested for the residual error estimations. The final model chosen by the applicant was based on an examination of residual plots, correlation plots (e.g. predicted concentration vs. observed concentration), minimum objective function (MOF), and validated with sensitivity and leverage analyses. The effect of Alimta was evaluated by adding Alimta as a dichotmous variable as described in equation 4. Covariates were retained if the difference in MOF ≥ 3.841 or more. Data were fit with NONMEM (ver 5.0).

The results of the modeling are listed in Table X. The parameters estimated from the JMCH database are similar to those estimated from the model building stage.

Table JMCH.11. Population LY231514 Pharmacokinetic Parameter Estimates (%SEE)

Parameter Description	Reference Dataset	Combined Dataset 2
Clearance		
TVCL, base parameter for CL (mL/min)	43.0 (16.6)	44.3 (13.1)
Θ_1, parameter for effect of CGCL on CL (mL/min)	47.2 (14.8)	43.0 (12.9)
CL (mL/min)=TVCL + Θ_1•CGCL/92.6	90.2	88.4[a]
Interpatient variability	19.3% (14.1)	18.3% (14.1)
Central Volume of Distribution		
TVV1, base parameter for V_1 (L)	6.13 (9.04)	6.34 (10.8)
Θ_2, parameter for effect of BSA on V_1	1.32 (11.6)	0.933 (18.3)
V_1 (L)=TVV_1•$BSA^{\Theta 2}$	12.7	11.0[b]
Interpatient variability	16.6% (29.3)	21.5% (21.9)
Intercompartmental Clearance		
Parameter for Q (mL/min)	14.5 (17.6)	22.7 (19.6)
Interpatient variability	NE	NE
Peripheral Volume of Distribution		
Parameter for V_2 (L)	3.38 (10.9)	4.39 (11.5)
Interpatient variability	24.5% (24.6)	22.8% (20.4)
Residual Error (proportional)	28.4% (8.20)	29.4% (7.12)

Abbreviations: NE = Not estimated, SEE = Standard error of the estimate.
[a] Median CGCL for Combined Dataset 2 = 94.9 mL/min.
[b] Median BSA for Combined Dataset 2 = 1.81 m^2.

The inclusion of cisplatin had no apparent effect on Alimta CL, as indicated by the results listed in Table X.

Table JMCH.12. Influence of Cisplatin as a Covariate Factor on LY231514 Pharmacokinetic Parameter Estimates (Combined Dataset 2)

	Parameter Estimate (SEE)	MOF[a]	ΔMOF
Parameter for effect of cisplatin on CL	0.978 (0.0310)	24136.726	-0.523
Parameter for effect of cisplatin on V_1	0.701 (0.0350)	24080.002	-57.247
Parameter for effect of cisplatin on V_2	0.985 (0.0421)	24137.245	-0.004

Abbreviations: MOF = Minimum objective function, NE = Not estimated, SEE = Standard error of the estimate.
[a] Reference MOF for Combined Dataset 2 = 24137.249.

Cisplatin does appear to affect V, although the significance of this effect is unclear. Vitamin supplementation did not significantly alter Alimta pharmacokinetics.

The parameter estimates for cisplatin PPK model are listed in Table X.

Table JMCH.15. Confidence Intervals (95%) for Cisplatin Population Pharmacokinetic Parameter Estimates

Parameter	Parameter Estimate	Calculated [a] 95% Confidence Interval Lower	Upper	Parameter Sensitivity 95% Confidence Interval Lower	Upper
Base parameter for CL (mL/min)	12.3	10.5	14.1	10.18	14.19
Base parameter for V_1 (L)	32.9	27.9	37.9	28.73	36.53
Q (mL/min)	312	226	398	266.9	382.6
V_2 (L)	52.0	47.4	56.6	48.35	55.99
Interpatient Variability on CL	0.172	0.0765	0.267	0.0881	0.3005
Interpatient Variability on V_1	0.144	0.0864	0.202	0.1014	0.21
Residual Error	0.0293	0.0234	0.0352	0.02506	0.03463

Abbreviations: CL = clearance, V_1 = central volume of distribution. Q = intercompartmental clearance. V_2 = peripheral volume of distribution.

[a] Standard calculation for 95% confidence interval: Parameter Estimate ± 1.96*Std. Error of Estimate from NONMEM results.

The sensitivity and leverage analyses suggest that the model is satisfactory. Inclusion of Alimta administration did not affect the model, suggesting that Alimta did not affect the pharmacokinetics of total platinum (difference in MOF of 0.506).

Reviewer Comments on Applicant's Modeling

- The applicant's approach to building ad validating the model was comprehensive and well-thought out. The list of covariates tested was extensive, and no covariates seemed to have been overlooked. The acceptance criteria for the model were also acceptable. Therefore, no additional modeling was deemed necessary.

- Although this model worked well for the studies used, it may be limited by the lack of patients with significant renal impairment. In the model building phase, the range of CLcr of the patients was from — ml/min (with only nine patients with a CLcr less than 50 ml/min). Therefore, this model may not be useful to assess Alimta in patients with significant renal impairment. Considering the results of the renal impairment study (JMAW), which included patients with renal function as low as 19 ml/min, the PPK model may not satisfactorily predict Alimta disposition in patients significant renal impairment (See figure x). This result may also be exacerbated by the use of a straight-line function to describe the Alimta pharmacokinetics. The influence of nonlinearity at lower renal functions may not be adequately modeled.

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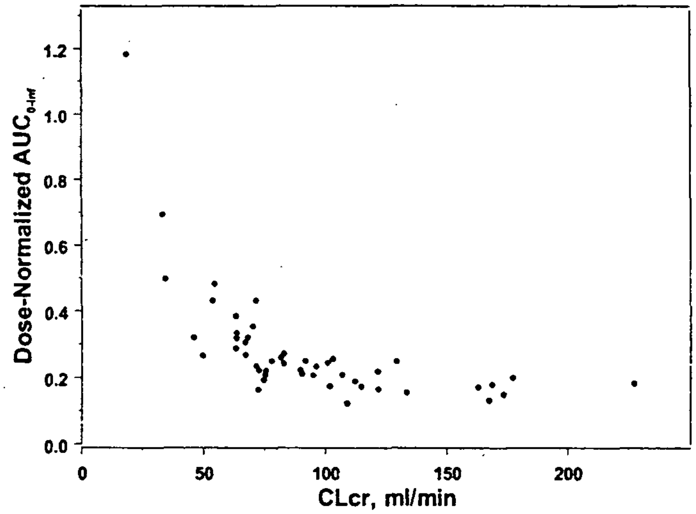


Figure 3. AUC_{inf} as a function of CL_{cr} from Study JMAW

- It is unclear why the applicant used the median Cl_{cr} of 107.4 for the combined dataset, and then reverted to the original value of 92.6 to assess the effect of cisplatin.

- No explanation for the 30% reduction in the volume of distribution of Alimta by cisplatin was offered by the applicant.

Pharmacodynamic Modeling

The most significant adverse event associated with Alimta is neutropenia. The applicant developed an exposure-response model to
- Characterize the time course of neutrophil response following Alimta
- Identify covariates that influence this model
- Characterize variability relative to absolute neutrophil counts
- Simulate the effect to covariates and dosing strategies on neutrophil count nadir.

Data

The patients from the same studies used to build the PPK model were used in these studies. The PPK model was used to estimate Alimta AUC, and neutrophil counts were taken from these patients at various times for up to 7 days post dosing. Data were available from 105 patients following the exclusion of missing or unevaluable data points.

The exposure–response model was a 2-compartment pharmacokinetic model (discussed above) linked to a 5-compartment model that described the pharmacodynamics of neutrophil circulation. The differential equations used are shown in Figure X.

$$\left.\begin{aligned}\frac{dX_1}{dt} &= -k_{12}\bullet X_1 + k_{21}\bullet X_2 - k_{10}\bullet X_1\\ \frac{dX_2}{dt} &= k_{12}\bullet X_1 - k_{21}\bullet X_2\end{aligned}\right\}\quad \text{(Plasma Concentration Time Profile)}$$

$$\frac{dStem}{dt} = k_{prol}\bullet Stem\bullet\left(1 - DS\bullet\frac{X_1}{V_1}\right)\bullet\left(\frac{BAS}{Circ}\right)^{FP} - k\bullet Stem \quad \text{(Stem Cell Compartment)}$$

$$\left.\begin{aligned}\frac{dM_1}{dt} &= k\bullet Stem - k\bullet M_1\\ \frac{dM_2}{dt} &= k\bullet M_1 - k\bullet M_2\\ \frac{dM_3}{dt} &= k\bullet M_2 - k\bullet M_3\end{aligned}\right\}\quad \text{(Maturation Compartments)}$$

$$\frac{dCirc}{dt} = k\bullet M_3 - k_{circ}\bullet Circ \quad \text{(Circulation Compartment)}$$

The effect of the drug is described the equation

$$\text{Stem Cell Proliferation Rate} = \underbrace{k_{prol}\bullet Stem}_{\text{Proliferation Rate Under Steady State Conditions}}\bullet\overbrace{\left(1 - DS\bullet\frac{X_1}{V_1}\right)}^{\text{Drug Concentration Effect}}\bullet\underbrace{\left(\frac{BAS}{Circ}\right)^{FP}}_{\text{Feedback Based Upon Circulating Neutrophil Counts}}$$

Where stem is the stem cell pool size,

Kprol is the stem cell proliferation constant
K is the maturation rate constant
BAS is the baseline neutrophil counts prior to drug
Circ is the neutrophil counts in circulation

DS: a linear proportionality constant relating drug concentration in the central compartment to cytotoxic effect on proliferation rate
FP is the feedback parameter that quantifies the strength of the feedback from CSF

The maturation time describes the time that the neutrophils spend maturing in the bone marrow before being released into the circulation. The mean transit time (MTT), the average time required to pass through the maturation chain is described as

$$MTT=(n+1)/k$$

Where n is the number of maturation compartments and k is the intercompartmental transfer rate constant.

Pharmacokinetic parameters were estimated from the PPK model. Bayesian estimates and dosing information were used to predict plasma concentrations in the PK/PD model. BAS, DS, FP and MTT were estimated in the model. FO estimation was used, and additive, proportional and combined residual error models were tested.

Table X lists the covariates that were tested.

Table POPD.8.3. Patient Factors Assessed as Potential Covariates in the Population PK/PD Analysis

Continuous Variables	Abbreviation	Categorical Variables	Abbreviation
Age	AGE	Gender	GEN
Albumin	ALB	Ethnic origin	ORIG
Body surface area	BSA	Alcohol use	ALC
Body weight	WT	Smoking status	SMK
Creatinine clearance (estimated by Cockcroft-Gault formula using age, weight, and serum creatinine)	CGCL	Treatment cycle	CYC
Total bilirubin	TBI		
Total protein	TPR		
Homocysteine	HCY		
Cystathionine	CYS		
Methylmalonic acid	MMA		
Methylcitrate I	MC1		
Methylcitrate II	MC2		
Total methylcitrate	MCT		

Each covariate was tested according to the three covariate models listed.

$$P = \Theta_1 + \Theta_2 \cdot COV$$
$$P = \Theta_1 \bullet (1 + \Theta_2 \cdot COV)$$
$$P = \Theta_1 \bullet COV^{\wedge}\Theta_2$$

Covariates that did not change MOF by ≥ 3.841 were not retained in the model. Once the final model was established, covariates were sequentially removed to determine the sensitivty of the model to the covariate. If the MOF changed by less than 10.828, the covariates were removed.

The model was validated by tested by predictive check, sensitivity analysis and leverage analysis similar the processes described for the PPK modeling.

The final model generated the following parameter estimates

Table POPD.9.12. Pharmacodynamic and Covariate Parameters in Final Population PK/PD Model for Neutrophil Response to LY231514 (PK/PD Dataset 2)

Parameter Description	Population Estimate (%SEE)*	Between-Patient Variability (%SEE)
Baseline Neutrophil Count		
TVBAS, parameter for BAS ($\times10^9$/L)	5.05 (4.83)	30.3% (32.7)
Θ_1, parameter for effect of CYS on BAS	0.00262 (23.0)	
Θ_2, parameter for effect of HCY on BAS	-0.102 (30.1)	
Mean Transit Time		
TVMTT, parameter for MTT (hr)	108 (2.45)	9.85% (28.7)
Θ_3, parameter for effect of ALB on MTT	0.824 (22.8)	
Dose Stimulus		
TVDS, parameter for DS	0.223 (6.01)	45.6% (29.0)
Θ_4, parameter for effect of TPR on DS	-0.00590 (25.1)	
Θ_5, parameter for effect of BSA on DS	-0.185 (25.5)	
Θ_6, parameter for effect of CYS on DS	0.000183 (35.3)	
Feedback Parameter		
TVFP, parameter for FP	0.190 (7.63)	27.6% (38.4)
Residual Error (proportional)	35.6% (11.3)	

Abbreviations: ALB = albumin; BAS = baseline absolute neutrophil count (that is, prior to LY231514 administration); BSA = body surface area; CYS = cystathionine; DS = dose stimulus parameter; FP = feedback parameter that quantifies the strength of the feedback action from the colony stimulating factors that regulate the physiologic process; HCY = homocysteine; hr = hour; MTT = mean transit time; SEE = standard error of the estimate; TPR = total protein; TVBAS = population estimate ("typical value") of baseline neutrophil count; TVDS = population estimate ("typical value") of dose stimulus; TVFP = population estimate ("typical value") of feedback parameter; TVMTT = population estimate ("typical value") of mean transit time.

*Estimation method: FO.

Parameters for covariate effects are centered on the median.

$BAS = TVBAS + \Theta_1 \bullet (CYS-228) + \Theta_2 \bullet (HCY-9.25)$

$MTT = TVMTT + \Theta_3 \bullet (ALB-35.0)$

$DS = TVDS + \Theta_4 \bullet (TPR-71.0) + \Theta_5 \bullet (BSA-1.81) + \Theta_6 \bullet (CYS-228)$

The ability of the model to predict ANC counts is demonstrated in Figure 4

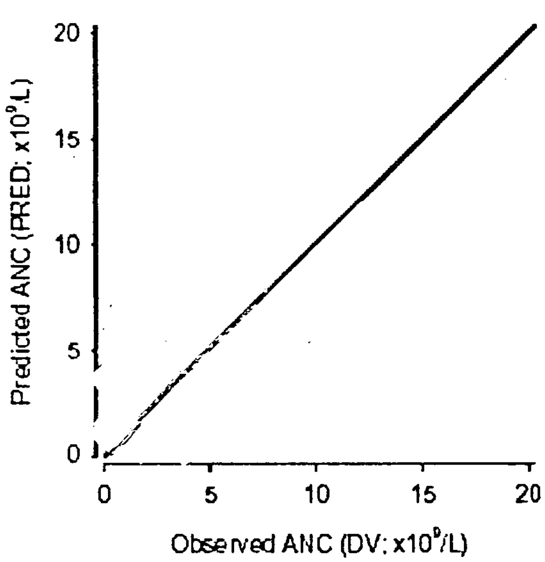


Figure 4. Individually-predicted vs observed ANC counts.

The covariates that influence the model are shown in Table X.

Table POPD.9.13. Impact of Covariates Included in the Final Population PK/PD Model on Model Parameters and on Clinically Relevant Features of the ANC-Time Profile (PK/PD Dataset 2)

Model Parameter	Effect of Model Parameter	Covariate	Effects Associated With Increased Neutropenia (↓NANC)
BAS	↓BAS ⇒ ↓NANC	cystathionine homocysteine	↓CYS ⇒ ↓BAS ↑HCY ⇒ ↓BAS
MTT	↓MTT ⇒ ↓ NANC, ↓T_{Nadir}	serum albumin	↓ALB ⇒ ↓MTT
DS	↑DS ⇒ ↓ NANC, ↑T_{Nadir}, ↑T_{Rcv}	serum total protein body surface area cystathionine	↓TPR ⇒ ↑DS ↓BSA ⇒ ↑DS ↑CYS ⇒ ↑DS

Abbreviations: ALB = serum albumin; BAS = baseline absolute neutrophil count (that is, prior to LY231514 administration); CYS = cystathionine; DS = dose stimulus parameter; HCY = homocysteine; MTT = mean transit time; NANC = nadir absolute neutrophil count; TPR = total protein.

The results indicate that the response to Alimta is directly affected by total serum protein, BSA and cystathionine (which ostensibly reflects folate status).

Using this model, the applicant simulated different scenarios to investigate the effect of different covariates on ANC nadir. The most significant results were obtained with the AUC, which indicated that ANC nadir decreases as AUC increases (see Figure 6).

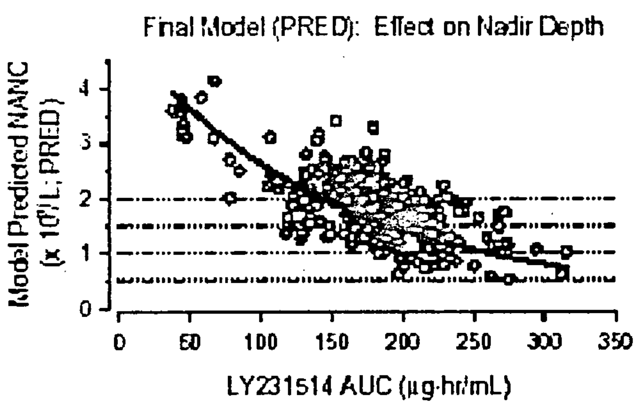


Figure 6. Predicted ANC nadir as a function of Alimta AUC (from applicant)

Applicant's conclusions

- A typical patient has 50% probability of remaining at CTC grade 0 following 500 mg/m^2 dosage of Alimta.
- Increased cystathionine and homocysteine reflect vitamin deficiency and are associated with lower ANC nadir.
- Lower BSA is associated with lower ANC nadir
- These results support the use of vitamin supplementation with Alimta.
- Alimta AUC had the greatest influence on ANC nadir; dosing based on renal function appears to offer the greatest control of hematological toxicity.
- These results suggest that dose reductions should be considered for low BSA patients and to control for hematological toxicities.

Reviewer's Response to the modeling.

- The model design, building and validation appear to be well-thought out, and mechanistically adequate to explain neutrophil behavior. No additional modeling was attempted.
- Although this appears to be an excellent modeling effort, Alimta was administered as a single agent. The neutropenic effect(s) of Alimta in combination with cisplatin cannot be assessed with this model.
- Further, as both AUC and CLcr had an impact on ANC nadir (AUC is dependent upon Clcr), the PPK modeling and by extension the PD modeling may not adequately quantify the relationships that occur in patients with more significant renal impairment.

Exposure - Response

Methods

FDA attempted to make correlations between Alimta exposure and effectiveness and Alimta and toxicity. The primary effectiveness endpoint was survival time (months), and best overall response (complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD)) is the secondary endpoint tested. Toxicity endpoints used in this analysis consisted of neutropenia, leukopenia, thrombocytopenia, stomatis, nausea, diarrhea vomiting, fatigue and pleural effusions(?).

Data

Pivotal effectiveness and safety data were derived from the pivotal clinical trial JMCH. Five hundred and seventy six patients were enrolled in the study. Following the removal of 128 patients with missing response, dosing or demographic data, 448 patients were available for evaluation. Approximately half of the patients were treated with 500 mg/m^2 of Alimta over 10 minutes, followed by 75 mg/m^2 of cisplatin, once every 21 days. Patients treated only with 75 mg/m^2 served as the active control. Dosing and demographic data files for the analysis were derived from a list of files submitted by the applicant (see appendix).

Exposure

The pivotal trials did not include any Zometa plasma concentration measurements. However, the PPK model from the preceding section predicts the plasma concentration very well. Hence, the pop PK model and its parameters were used to predict the typical AUC values given the dosing regimen in the clinical studies. The AUC represents the average overall exposure in these patients. Some patients received dose reductions of Alimta in later (different) cycles of treatment (36 patients). Therefore, median Alimta dose per patient was used in these analyses.

Effectiveness Endpoint

Correlations of Alimta with survival time were modeled using Cox proportional hazard regressions. Correlations of Alimta with response variables were conducted as logisitic regressions. The survival data from JMCH is shown in Table X (reproduced from the FAD Statistical review for Alimta).

Table 1. Primary Endpoint: Survival for RT Population (FDA Analysis)

	RT Population (N=448)		FS Population (N=331)		PS+NS Population (N=117)	
	LY/cis (N=226) n (%)	Cisplatin (N=222) n (%)	LY/cis (N=168) n (%)	Cisplatin (N=163) n (%)	LY/cis (N=58) n (%)	Cisplatin (N=59) n (%)
Patients dead[a]	145 (64)	159 (72)	95 (57)	103 (63)	50 (86)	56 (95)
Survival time (months)						
Median	9.9	8.5	10.1	8.7	9.4	7.2
Range	0.1–29.2	0.4–28.0	0.1–25.9	0.5–23.7	0.3–29.2	0.4–28.0
p-value[b]						
Long-rank	0.021		0.051		0.253	
Wilcoxon	0.028		0.039		0.440	
Hazard Ratio[c]	0.766		0.758		0.798	
95% CI for Hazard Ratio[c]	(0.61, 0.96)		(0.57, 1.0)		(0.54, 1.17)	

Statistical reviewer's results based on the analysis data sets provided by the sponsor.
[a] Patients were died for different reasons: study disease related, study toxicity, and other causes.
[b] P-value is based on the test results for the two treatment groups.
[c] Hazard Ratio is based on the proportional-hazards model with the treatment as single independent variable.

Toxicityy Endpoint

Corrleations between Alimta and toxicity endpoints were conducted as logisitic regressions with the parameters tested.

All analyses were conducted using SAS (6.12).

Results and Discussion

Effectiveness

The results of the survival correlations are listed in Table X.

Table X.

Parameter	N	Estimate	P-value	Hazard Ratio
Alimta	**448**	**-0.257**	**0.026**	**0.773**
Alimta/vitB12	**448**	**-0.314**	**0.011**	**0.731**
CR	**448**	**-12.8**	**0.96**	**0.0**
PR	**448**	**-1.365**	**<0.0001**	**0.255**
SD	**448**	**-0.455**	**0.0085**	**0.634**
PD	**448**	**0.301**	**0.16**	**1.3652**

Survival was positively correlated with Alimta, especially if supplemented by folic acid/vitamin B12. In both cases, the hazard ratio (HR) is appreciably decreased relative to patients not treated with Alimta. Alimta dose and AUC were also positively correlated with survival ($p<0.05$), but the HR is not appreciably affected (HR was ~1 for all three parameters tested). The reason for these findings is likely that these parameters are somewhat confounded; only a narrow range of doses were administered in the trial (resulting in a relatively narrow range of AUCs, which is dependent upon Clcr), and they are positively correlated because they are elements of having, or not having, received Alimta. No correlation was observed for gender, age or race.

Partial response (PR) and stable disease (SD) as assessed by an independent evaluator are both highly correlated with survival (independent of dose; data not shown). These data suggest that that PR and SD are good prognostic indicators for survival, this possibility should be investigated further. Progressive disease (PD) is not correlated with survival, the reason for which is unclear. Surprisingly, complete response (CR) does not correlate with survival. The reason for this is probably because only 2 patients exhibited CRs.

Safety

The results of the safety correlations are shown in Table X.

Adverse Event	**N**	**Alimta Dose, P**
Neutropenia	354	0.0011
Leukopenia	354	0.0001
Thrombocytopenia	448	0.0003
Vomiting	354	0.0004
Diarrhea	334	0.001
Nausea	354	0.34

All adverse events are grade 3 or 4.

These data indicate that Alimta use was significantly associated with hematological sequelae, as well as vomiting and diarrhea. Again AUC seems to be confounded with Alimta use, and it is difficult to conclude much regarding concentration and adverse events. Again, it appears that because of the narrow range of doses employed, AUC does not explain the probability of toxicity any more than dose.

Effect of Alimta on Renal Function

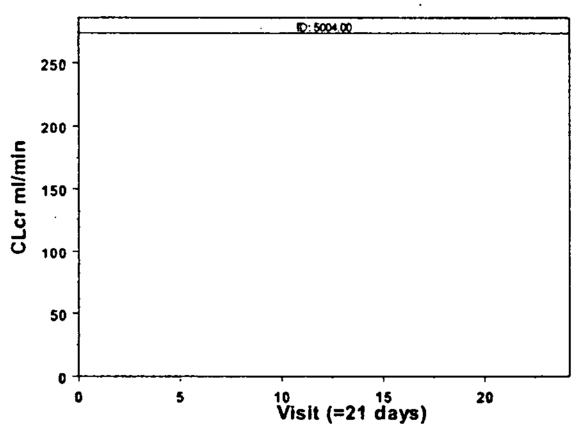
Based on the preliminary plot of CLcr as a function of patient visit from JMAW (see Figure 3), the time course of CLcr following Alimta administration was evaluated for JMAW and JMCH.

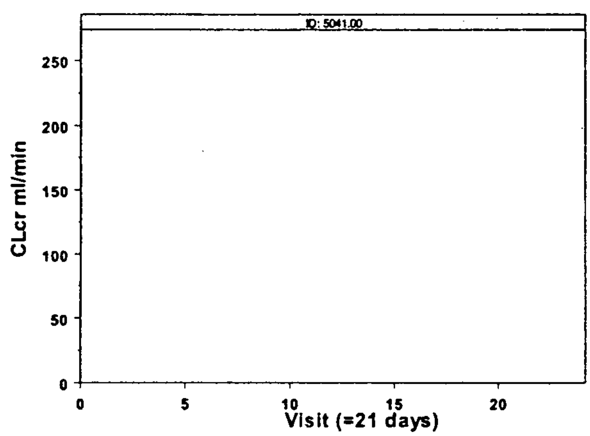
Data

The data used in the analysis was from the renal impairment study JMAW, where Alimta was administered as a single agent at 500 or 600 mg/m^2 once every three weeks, and from pivotal clinical trial JMCH (described above).

Results

The decline in CLcr can be observed in the following figures (figure 8a, b, c) for study JMAW.





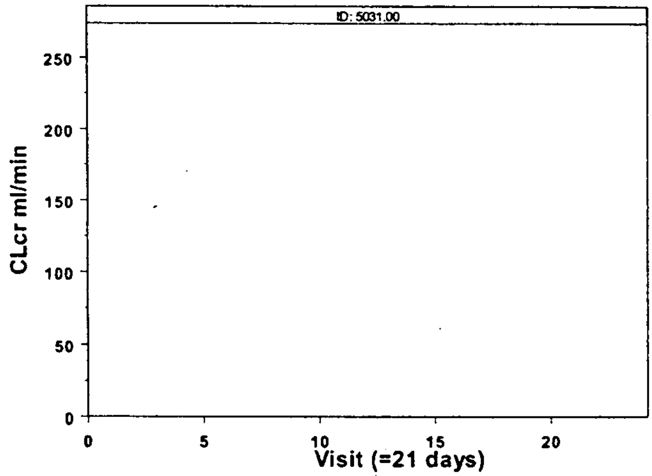


Figure 4. Clcr in patients treated with Alimta (dotted line: observed data; solid line, population estimate)

Figure 4 shows that over time, Clcr decreased with Alimta use. However, this trend was not observed in the pivotal clinical trial JMCH, as indicated by the results exemplified by several patients (see Figure 5).

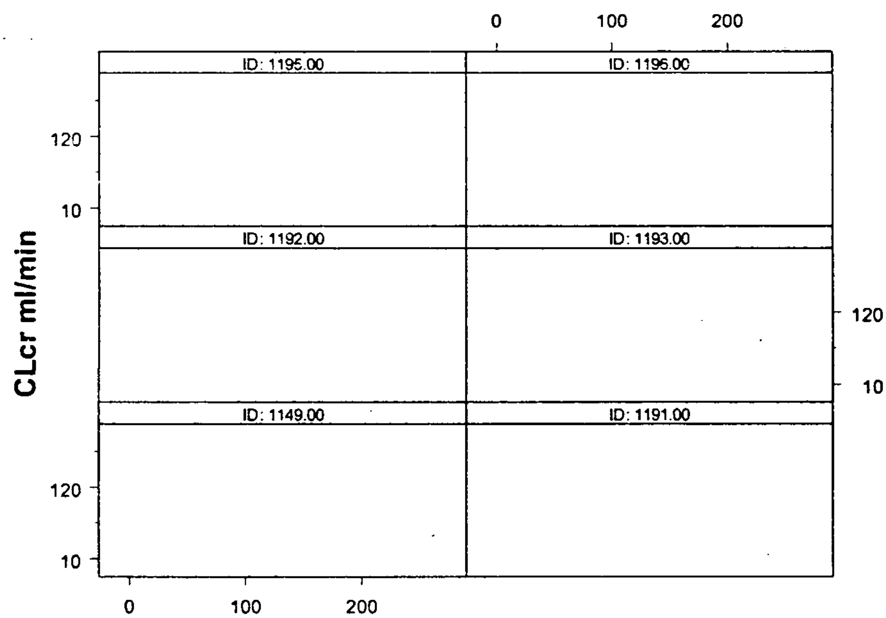


Figure 5. Clcr in patients treated with Alimta in study JMCH (blue dots observed data)

Conclusions

1. The data demonstrate a gradual decrease in CLcr over time with Alimta treatment in the renal impairment study (JMAW), but was not observed in the pivotal clinical trial (JMCH), despite patients being co-treated with cisplatin, which itself is renal toxic. The reason for this discrepancy may be the steps prescribed in the JMCH protocol to adjust doses or delay doses based on toxicity. Further, there was only one patient in study JMCH whose Alimta dose was reduced due to a reduction in creatinine clearance. A potentially confounding issue is that the patients predominantly had very high renal function; therefore, small changes in creatinine clearance that resulted in a lower value within the defined normal range may not have prompted dose modification.

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Exposure – Response: Overall Conclusions

1. The population pharmacokinetic modeling conducted by the applicant appears well-founded and describes the behavior of Alimta over the range of creatinine clearances recruited into the study (approximately ≥ 50 ml/min). However, the model may not adequately characterize Alimta in patients with moderate or severe renal impairment. The renal impairment study showed a curvilinear relationship between AUC and CL, which differs from the population model with showed a linear relationship between CLcr and CL. Therefore, the model may not adequately capture this nonlinearity.

2. The population pharmacodynamic modeling conducted by the applicant appears well-founded and describes the behavior of Alimta alone. Alimta is co-administered with cisplatin, which also causes myelosuppression, and is renally toxic (which would cause further increases in Alimta concentrations and produce more neutropenia). Therefore, co-administration of cisplatin can reasonably be expected to exacerbate the toxicity of Alimta as a single agent.

3. The survival advantage of Alimta was clearly linked to its use. However, likely as result of the limited range of doses, no exposure-response relationship could be obtained for effectiveness or safety endpoints.

4. Partial response and stable disease were also correlated with survival, suggesting that they may be good prognostic indicators in this disease.

5. The preliminary analysis and the population model of CLcr in patients in the renal impairment study indicates that CLcr may decrease gradually over time. Therefore, it may be prudent to assess renal function (by Cockcroft-Gault) before administration of each dose of Alimta

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Appendix E. NDA Filing form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-462	Brand Name	Alimta
OCPB Division (I, II, III)	I	Generic Name	Pemetrexed;MTA
Medical Division	Oncology HFD-150	Drug Class	
OCPB Reviewer	Brian Booth	Indication(s)	With cisplatin for malignant mesothelioma
OCPB Team Leader	Atik Rahman	Dosage Form	Intravenous
		Dosing Regimen	10 min infusion
Date of Submission	10/24/02	Route of Administration	Intravenous
Estimated Due Date of OCPB Review	11/15/03	Sponsor	Eli Lilly
PDUFA Due Date	NOT FILED.	Priority Classification	Rolling/Fast track/P
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	na			
Blood/plasma ratio:	na			
Plasma protein binding:	x	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	na			
multiple dose:	na			
Patients-				
single dose:	x	10		
multiple dose:	x	1		
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	7		
In-vivo effects of primary drug:	x	2		
In-vitro:	x	1		
Subpopulation studies -				
ethnicity:	x	1		
gender:	x	1		
pediatrics:	na			
geriatrics:	x	1		
renal impairment:	x	1		
hepatic impairment:	na			
PD:				
Phase 2:	na			
Phase 3:	x	1		
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	10		
Phase 3 clinical trial:	na			
Population Analyses -				

Data rich:	x	1		
Data sparse:	x	1		
II. Biopharmaceutics				
Absolute bioavailability:	na			
Relative bioavailability -				
solution as reference:	na			
alternate formulation as reference:	na			
Bioequivalence studies -				
traditional design; single / multi dose:	Na			
replicate design; single / multi dose:	na			
Food-drug interaction studies:	na			
Dissolution:	na			
(IVIVC):	na			
Bio-wavier request based on BCS	na			
BCS class	na			
III. Other CPB Studies				
Genotype/phenotype studies:	na			
Chronopharmacokinetics	na			
Pediatric development plan	na			
Literature References	4-5			
Total Number of Studies		4-5		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	x	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is there any pk/pd correlations in pivotal clincal trial (FDA analysis)? Is there any significant renal impairment? Are there any significant drug-drug interactions?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR

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/s/

Brian Booth
12/4/03 03:12:21 PM
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Roshni Ramchandani
12/4/03 03:23:07 PM
BIOPHARMACEUTICS

Atul Bhattaram
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