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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-462

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-462 AMENDMENT

Drug:	**ALIMTA**
Generic name:	Pemetrexed; N-[4-[2-(2-amino-3,4-dihydro-4-oxo-7H-pyrrolol[2,3-d]pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid; MTA; LY231514;
Formulation:	40 ml solution of 200 or 1000 mg for intravenous infusion; lyophilized powder of 20, 100 and 500 mg for reconstitution and intravenous infusion.
Indications:	ALIMTA plus cisplatin for the treatment of patients with malignant pleural mesothelioma.
Applicant:	Eli Lilly and Company Indianapolis, IN 46285
OCPB Division:	Division of Pharmaceutical Evaluation 1 (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	10/24/02; 12/06/02; 03/24/03; 9/4/03; 9/9/03; 9/16/03; 10/7/03
EDR e-Files:	**See Appendix for EDR files**

Primary/Pharmacometric Reviewer: Brian Booth, Ph.D.

Pharmacometrics: Roshni Ramchandani, Ph.D.; Atul Bhattram, Ph.D.

Pharmacometric Team Leader:	Joga Gobburu, Ph.D.
Team Leader:	N.A.M. Atiqur Rahman, Ph.D.
Type of Submission:	NDA-New Molecular Entity

I. Executive Summary

This amendment incorporates the correction of a typographical error in the "Recommendations" section of the original review. The applicant is seeking marketing approval for Alimta in combination with cisplatin for the treatment of patients with

unresectable malignant mesothelioma (or patients who are not surgical candidates for malignant mesothelioma). The applicant demonstrated a survival advantage with Alimta and cisplatin in comparison to cisplatin alone.

Recommendation: The Alimta NDA 21-462 is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Phase 4 Commitments:

No phase 4 commitments are recommended.

/S/

Reviewer: Brian Booth, Ph.D.

/S/

Team Leader: NAM Atiqur Rahman, Ph.D.

CC: NDA 21-462
HFD-150/Division File
HFD-150/PGarvey, MHazarika, Bwhite, JohnsonJ
HFD-860/MehtaM, Csahajwalla, RahmanNAM, GobburuJ, BoothB
CDR/Biopharm

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/s/

Brian Booth
12/23/03 01:30:28 PM
BIOPHARMACEUTICS

Mehul Mehta
12/23/03 02:20:36 PM
BIOPHARMACEUTICS

II. Table of Contents

III. Summary of Clinical Pharmacology Findings

Alimta is a novel antimetabolite that inhibits thymidylate synthase, dihydro folate reductase and glycinamide ribonucleotide formyl transferase, and mediates cell death by inhibiting DNA synthesis. Alimta plus cisplatin mediates a survival advantage compared to cisplatin alone in malignant mesothelioma. The main toxicity of Alimta is neutropenia, but leukopenia, thrombocytopenia, stomatitis, vomiting diarrhea and nausea were also noted. The pharmacokinetics of Alimta follow a 2-compartment model, and excretion is predominantly renal. Alimta was not metabolized by any cytochrome P-450, nor did it inhibit any cytochrome P-450 isozyme. Total systemic clearance of Alimta is 91.8 ml/min and is well correlated with glomerular filtration rate and creatinine clearance (CLcr) calculated using the Cockcroft-Gault formula. The elimination half-life is 3.5 hours, and no accumulation was noted. The pharmacokinetics of Alimta were not affected by sex, age or ethnicity. Co-administration of cisplatin did not alter the pharmacokinetics of Alimta, or vice versa. Co-administration of carboplatin did not alter the pharmacokinetics of Alimta, but the pharmacokinetics of carboplatin may have been affected. Folic acid/vitamin B12 did not alter the pharmacokinetics of Alimta, nor did aspirin at doses of 1.3 mg/day. However, ibuprofen increased Alimta AUC by approximately 20% at a moderate dose of 1.6 gm/day. Moderate doses of aspirin (1.3 mg/day) did not affect the pharmacokinetics of Alimta. AspisirnRenal impairment studies of Alimta as a single agent indicated that the Alimta AUC increased by 130% in patients with moderate renal impairment (CLcr 30-50 ml/min; n=6), suggesting that neutropenia might be exacerbated in these patients.

IV. Question Based Review

A. General Attributes

What are the highlights of the chemical properties of drug substance and formulation of the drug product?

Alimta (pemetrexed;MTA;LY231514) is antifolate antineoplastic agent similar to methotrexate. The chemical name for ALIMTA is N-[4-[2-amino-4,7-dihydor-4-oxo-1H-pyrrolo [2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid disodium salt, which has a molecular weight of 597.49. The chemical structure is shown in Figure 1.

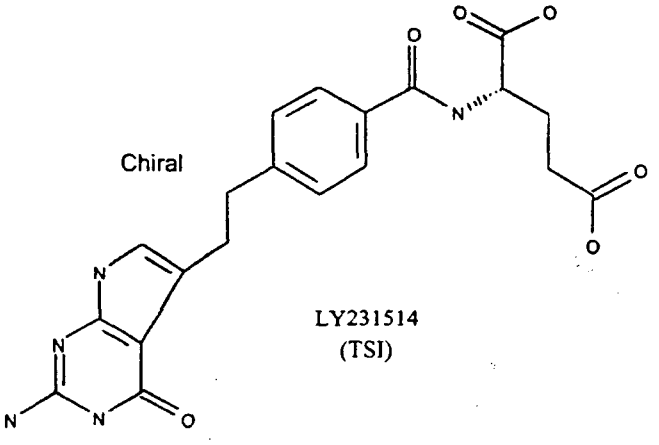

Figure 1. The chemical structure of Alimta

Alimta is available as a lyophilized powder containing 500 mg of Alimta and 500 mg of mannitol. Vials are reconstituted with 20 ml of 0.9% saline (USP) and pH may be adjusted with hydrochloric acid or sodium hydroxide.

What is the therapeutic indication and proposed dosage regimen of Alimta?

Alimta in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are not candidates for curative surgery. The proposed dosing regimen is 500 mg/m2 of Alimta infused over ten minutes, which is followed 30 minutes later with an infusion of 75 mg/m2 cisplatin over two hours once every 21 days. Treatment is to be preceded with 5 daily oral doses of folic acid and one intramuscular vitamin B12 injection. Vitamin B12 should be repeated once every three cycles. Folic acid should continue during the full course of therapy and for 21 days after the last dose of Alimta.

What is the putative mechanism of action of Alimta?

Alimta inhibits thymidylate synthase (TS), which is essential for with DNA synthesis, and thereby mediates its cytotoxic activity. Alimta also inhibits dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT) (See Figure 2).

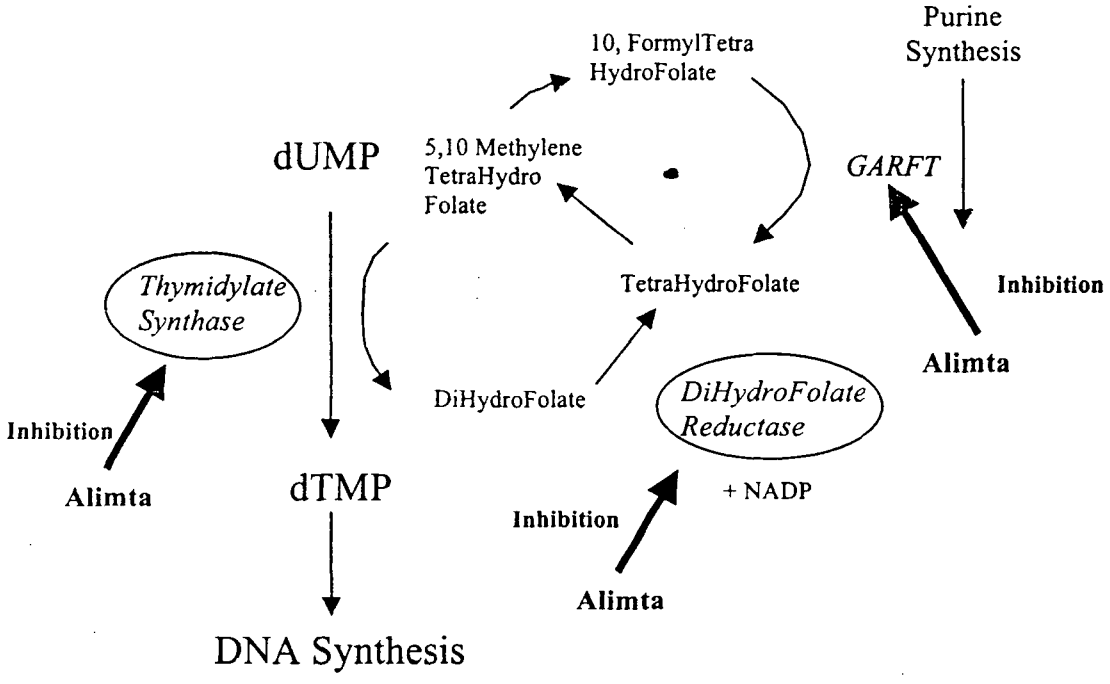

Figure 2. Mechanisms of action for Alimta.

What effectiveness and safety information contributes to the assessment of the clinical pharmacology data?

The effectiveness of Alimta in the pivotal clinical trial was based on prolonging survival. In a study of 574 patients with malignant mesothelioma, 448 were evaluable for response. The secondary endpoint was response rate. Toxicity (adverse events) that were assessed for Alimita were neutropenia, leukopenia, thrombocytopenia, stomatitis, diarrhea, nausea and vomiting.

B. General Clinical Pharmacology

What are the effectiveness and safety endpoints?

The primary clinical endpoint in the pivotal trial of Alimta plus cisplatin vs cisplatin alone was survival. Best overall responses were the secondary endpoint for this study. Responses were defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) based on tumor size assessed by CAT scan. Two hundred and twenty six patients were treated with 500 mg/m2 of Alimta and 75 mg/m2 of

cisplatin in the first cycle, compared to 222 who received 75 mg/m2 cisplatin alone. Thirty-six patients had their doses of Alimta reduced at various cycles.

What are the active moieties in the plasma?

Alimta itself is the active moiety. Alimta does not appear to be metabolized to any appreciable extent, and it is almost completely excreted intact in urine.

What are the characteristics of the exposure-response relationships of Alimta?

Effectiveness

In the pivotal phase 3 trial, only one dose of Alimta was administered. Consequently, no concentration-effect relationships could be determined because of the narrow range of doses and AUCs available in this study. However, proportional hazards regressions indicated that survival was significantly correlated with Alimta treatment, especially if the patients were supplemented with folic acid/vitamin B12. Furthermore, complete and partial responses and stable disease were also correlated with Alimta use.

Toxicity

Neutropenia
The main toxicity associated with Alimta was hematological. Neutropenia was the most significant toxicity, and was the main cause of dose reductions in the trial (9 of 36 cases). Alimta was significantly correlated with neutropenia leukopenia, thrombocytopenia, vomiting, and diarrhea.

The applicant modeled neutropenia in response to single-agent Alimta (based on data from eight phase 2 studies). Simulations with this model suggested that neutropenia will

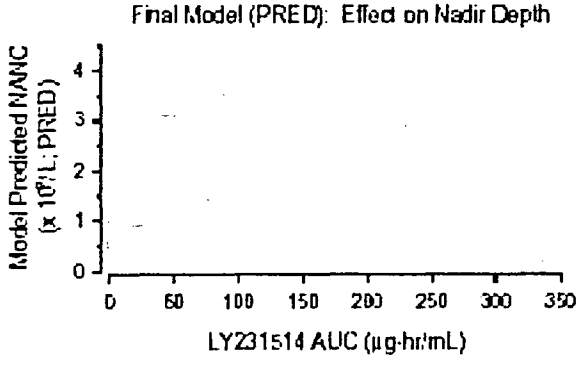

Figure 3a. Simulations of nadir ANC in patients treated with single –agent Alimta. (from applicant)

increase as AUC increases. These predictions are relatively consistent with the clinical findings, however, the predictive ability of this model is limited by the use of single-agent Alimta, and patients with relatively high renal function (>50 ml/min, mild impairment to normal). As cisplatin itself causes neutropenia, and renal function is related to Alimta AUC, it would be expected that neutropenia would be more severe with Alimta and cisplatin co-administration.

Renal toxicity

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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The pharmacokinetics of Alimta were linear up to dosages of 700 mg/m2.

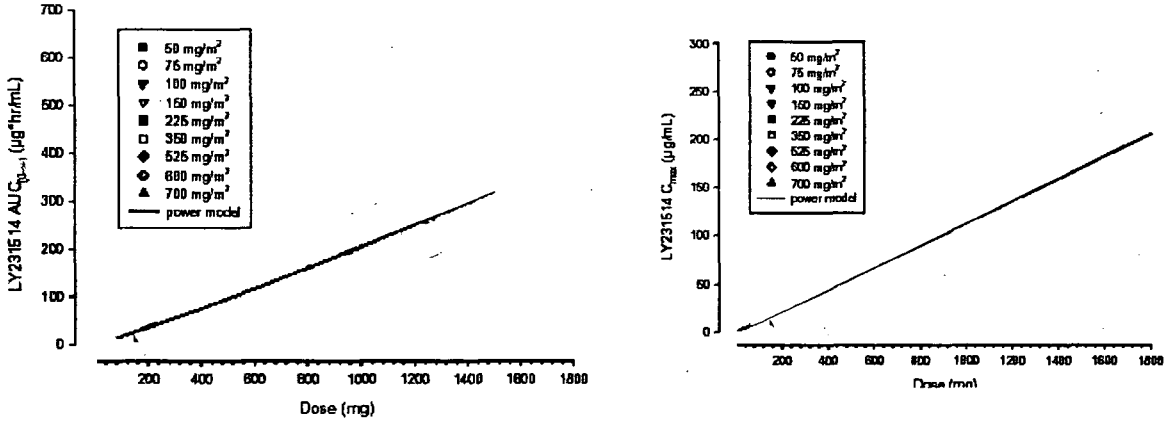

Figure 4. Linearity of Alimta AUC and Cmax (from applicant)

The pharmacokinetics were described by a two-compartment model. Clearance is 91.8 ml/min, volume of distribution is 16.1 L and the elimination half-life of Alimta is 3.5 hours (see figure 5).

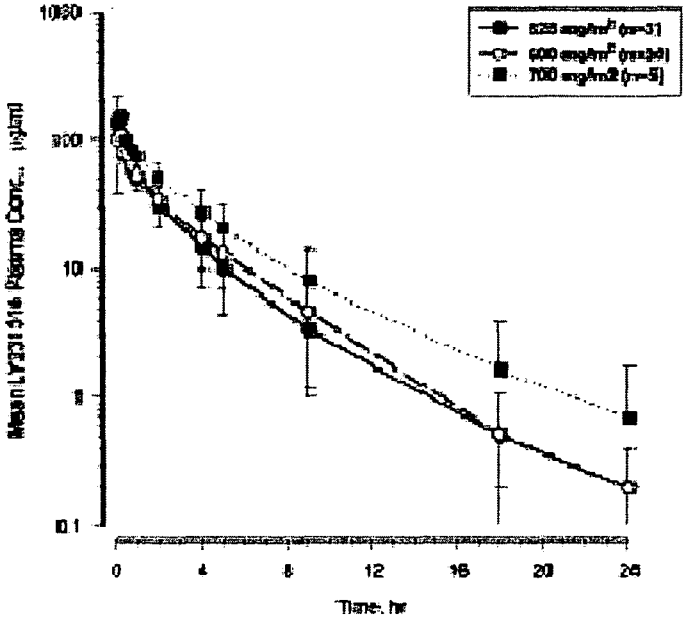

Figure 5 Plasma concentration-vs-time curve for Alimta (from applicant)

Excretion of Alimta was predominantly renal, and completed within 24 hrs.

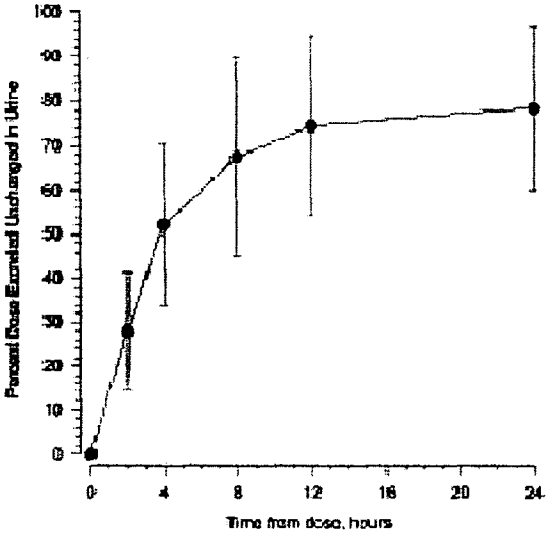

Figure 6. Urinary accumulation of Alimta (from applicant)

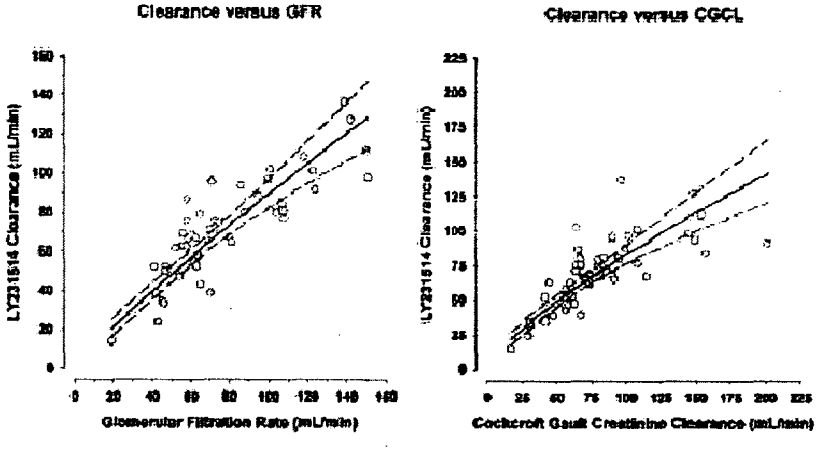

Figure 7. Alimta systemic clearance as a function of GFR and CLcr (from applicant)

Clearance of Alimta was well-correlated with renal function. Protein binding was approximately 80 % over a range of 5 to 200 μg/ml (ADME14), and was unaffected by mild or moderate renal impairment (JMAW).

C. Intrinsic Factors

Does renal impairment affect the pharmacokinetics and pharmacodynamics of ALIMTA?

The sponsor conducted a renal impairment study in patients with advanced cancer (JMAW). ALIMTA was administered as a 500 or 600 mg/m2 infusion over 10 minutes. Glomerular filtration rate was measured in patient using Tc99m-DPTA, and creatinine clearance was calculated using the Cockcroft-Gault equation (CLcr) and CLcr using lean body mass (CLBM). Dense sampling was conducted over 72 hours in the first cycle of therapy. Data from forty-seven patients was used in the analysis. The sponsor demonstrated that the CLcr provided a good approximation of measured renal function (GFR) as shown in Figure 8.

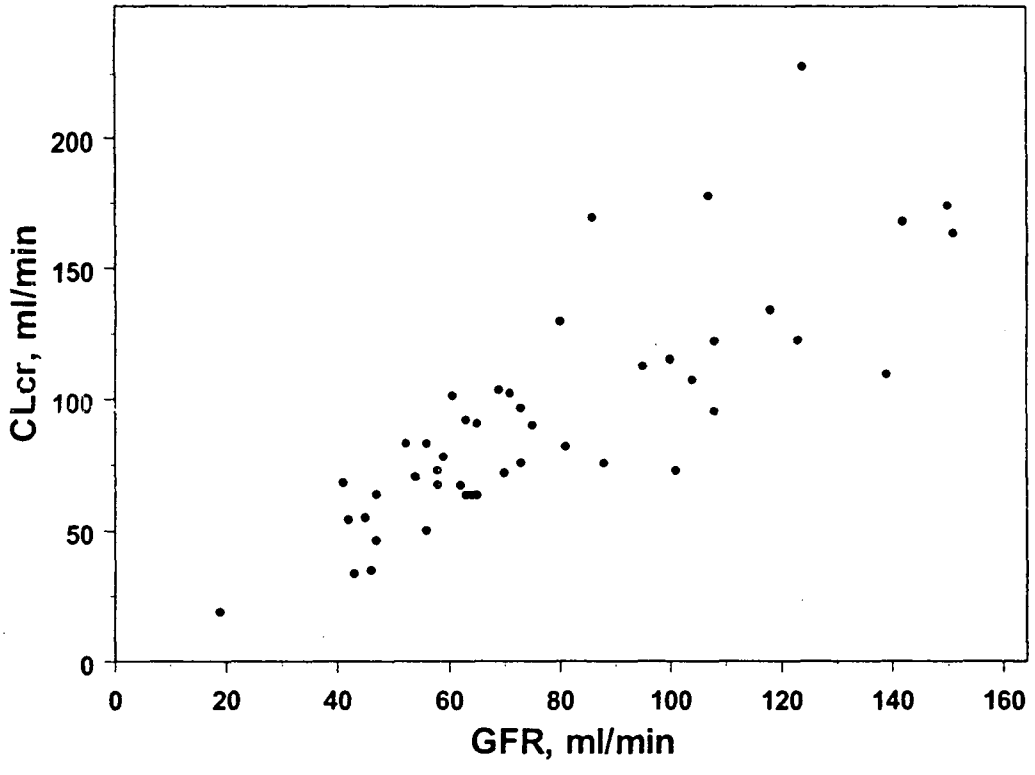

Figure 8. The relationship of creatinine clearance (CLcr) versus measured renal function (GFR; FDA analysis).

According to the sponsor's stratification, (upper normal >80 ml/min, lower normal 60-79 ml/min, moderate 40-59), a 5 to 9-fold difference in ALIMTA CL can be expected between normal and severe impairment. Folic acid and vitamin B12 had no apparent effect on ALIMTA pharmacokinetics. Despite the range in CL, the sponsor reported that ALIMTA was well tolerated, and concluded that no dose modifications were necessary in these patients with moderate to normal renal function. The only patient with severe renal impairment (CLcr 19 ml/min) died from drug related toxicity.

These analyses were conducted with patients who were stratified by GFR. However, in practice, patients will be stratified by CLcr. Therefore, these data were re-analyzed accordingly, and stratified according to the renal impairment criteria promulgated by the FDA guidance. According to this analysis, ALIMTA AUC varied with renal function according to a curvilinear relationship (Figure 9).

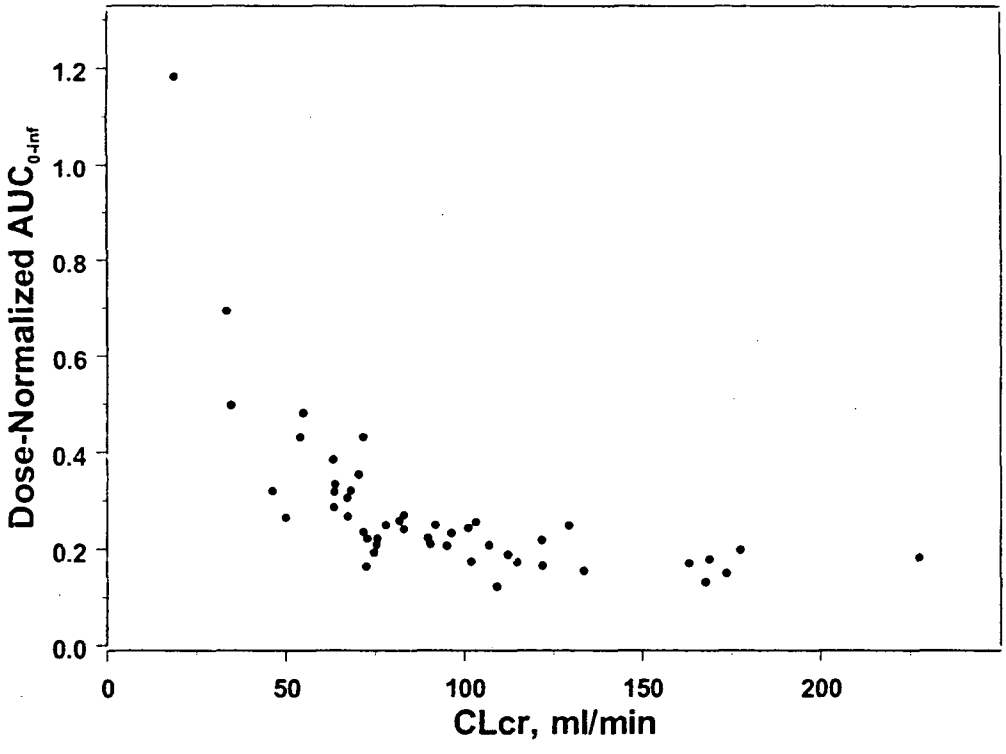

Figure 9. ALIMTA AUC_{inf} in patients with varying renal function (CLcr; FDA analysis).

The ALIMTA Cmax and AUC_{inf} for patients with different renal function are listed in table 1.

TABLE 1. ALIMTA C_{max} and AUC in patients with Renal Impairment (FDA Analysis)

Renal Function	N	C_{max} (dose-normalized)	AUC (dose-normalized)	% change
Normal > 80 ml/min	21	0.130 ± 0.044	0.193 ± 0.039	NA
Mild 50-80 ml/min	20	0.122 ± 0.054	0.274 ± 0.068	42.0 ↑
Moderate 30-50 ml/min	6	0.136 ± 0.083	0.448 ± 0.151	132 ↑
Severe <30 ml/min	1*	0.088	1.182	512 ↑

*Patient died from drug-related toxicity

Using the CLcr and FDA criteria, the ALIMTA AUC_{inf} increased more than 40% in patients with mild impairment, and 132 % in patients with moderate impairment. The variability is relatively constant (20-30%) across the groups, suggesting that the mean AUC_{inf} estimates are likely fairly accurate. However, there are only six patients with moderate renal impairment, which is likely too few to adequately assess toxicity. Two additional issues need to be considered. First ALIMTA is indicated for use in combination with cisplatin, which itself induces renal toxicity and could reasonably be expected to exacerbate any ALIMTA toxicity in patients with renal impairment. This possibility was not addressed in these studies and the need for dose reductions in patients with renal impairment should be addressed. Secondly, the effect of this combination should be addressed in multiple cycles of therapy because cisplatin toxicity is generally manifested after several cycles of therapy. Moreover, the mean renal function in these patients appeared to decline with each visit (see figure 10). Although this decline in renal function may have resulted from patients' diseases, it may also have resulted from ALIMTA.

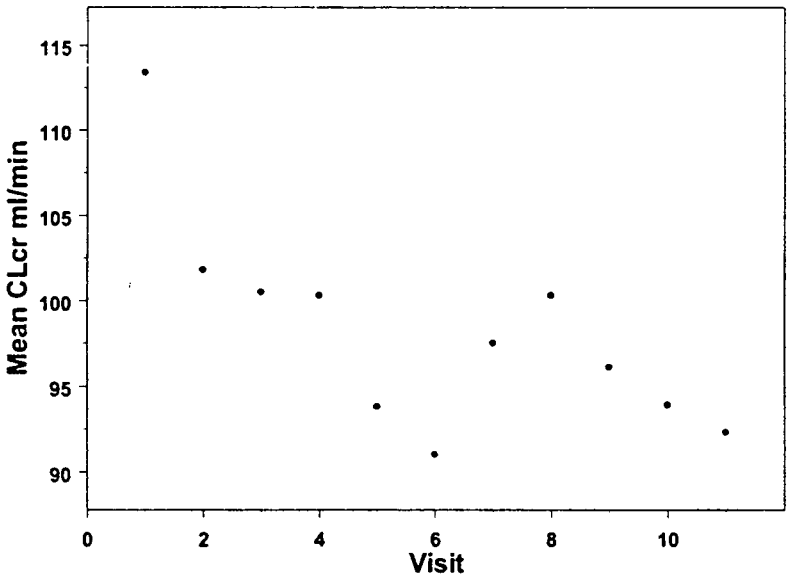

Figure 10. Mean Renal Function per visit (FDA analysis).

A similar phenomenon was observed for some patients treated with ALIMTA and Cisplatin (see figure 11).

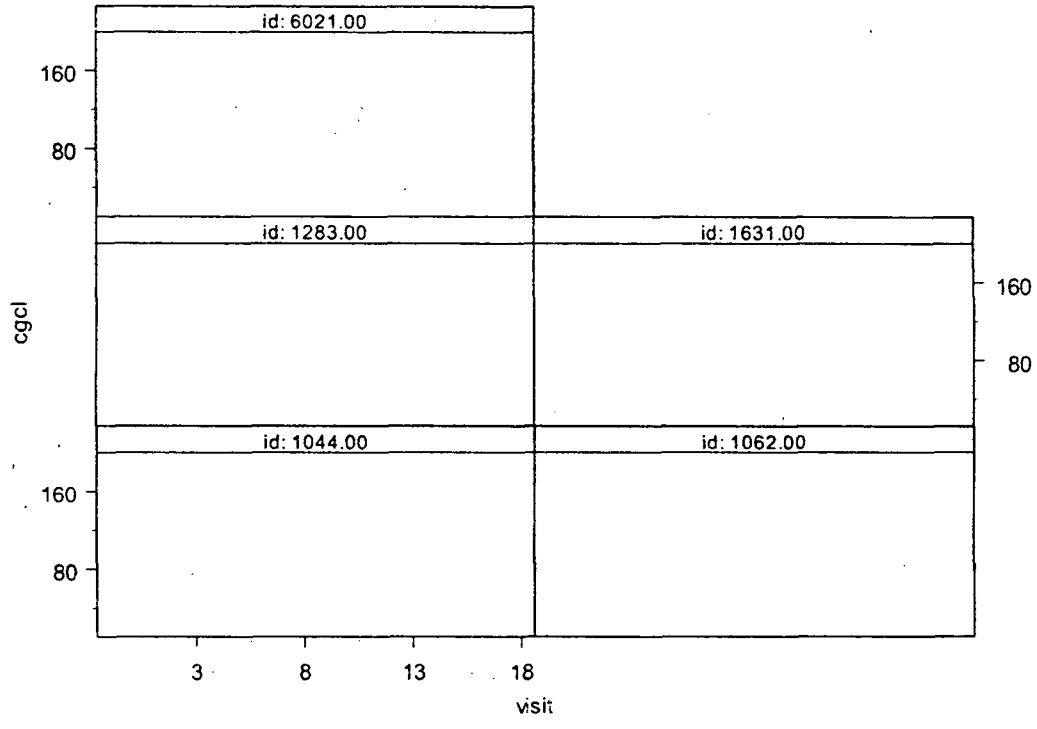

Figure 11. Renal function by visit from several patients in study JMCH (FDA analysis).

Gender did not appear to have any significant effect on ALIMTA exposure.

D. Extrinsic Factors

Is MTA involved in any significant Cycotchrome P-450 based drug-drug interactions?

MTA does not appear to undergo metabolism to any significant extent, and plasma concentrations of ALMITA are not subject to modulation by inhibitors or inducers of cytochrome P-450 (CYP 450). Furthermore, in vitro studies indicate that ALIMTA does not significantly inhibit CYP 3A4, 2D6, 2C9 or 1A2. Therefore, ALIMTA is not expected to affect the disposition of co-administered medications that are metabolized by CYP 450 via enzyme inhibition. The potential of ALIMTA to induce CYP 450 isozymes

has not been determined, therefore it remains unknown whether MTA might cause a drug-drug interaction based on CYP 450 enzyme induction.

Is MTA metabolized?.

No. MTA does not appear to undergo significant metabolism. Preclinical mass balance studies indicated that the greatest amount of the radio-labeled species excreted in the urine was unchanged parent (>90% of the administered dose; ADME report 15). The only metabolite identified in preclinical studies, LY368942, was not detected in humans. In humans, unchanged MTA was the major species detected in urine. A metabolite, LY338979 accounted for less than 5% of the species detected (based on ion intensity), and there were trace quantities of several other metabolites that could not be identified (ADME report 15).

Does MTA inhibit cytochrome P-450 isozymes?

The sponsor tested whether MTA inhibits cytochrome P-450 (CYP450) isozymes 3A, 2D6, 2C9 and 1A2, by incubating MTA with microsomes that specifically expressed each CYP 450 isozyme. Microsomes were incubated with MTA in concentrations up to 1000 uM (5.79 ug/ml). CYP 3A was inhibited by approximately 20% at an MTA concentration of 530 ng/ml. However, this is likely not significant because the MTA Cmax following the prescribed 500 mg/m2 dose of MTA is approximately 100 ng/ml. CYPs 2D6, 2C9, 1A2 were not significantly affected by MTA at even higher concentrations (see Table 2).

Table 2. In Vitro Inhibition of CYP 450 Isozymes by MTA

LY231514 Concentration μM (ng/ml)	CYP 450 Isozyme	Metabolism % of Control
885 (530)	3A*	79
1000 (597)	2D6!	106
1000 (597)	2C9†	93
1000 (597)	1A2@	92

*as measured by midazolam metabolism to 1'-hydroxymidazolam
! as measured by bufurolol metabolism to 1'-hydroxybufurolol
† as measured by diclofenac metabolism to 4'-hydroxydiclofenac
@ as measured by phenacetin metabolism to acetominophen

Does MTA induce cytochrome p-450 isozymes?

This question remains unanswered because the applicant did not conduct any in vitro studies to address this question. The applicant indicated that enzyme induction seems unlikely because 500 mg/m2 ALIMTA is administered as a 10-minute infusion once every 21 days for mesothelioma, and enzyme induction generally requires a more prolonged incubation.

Is MTA involved in any significant Non-CYP-450 based drug-drug interactions?

MTA is predominantly eliminated by renal excretion. Therefore, some of the co-administered medications may be affected by MTA, and/or vice versa. The sponsor investigated the effect of co-administering MTA with cisplatin or carboplatin, and nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen, and the effect of simultaneously administered vitamins.

Cisplatin

The potential interactions between cisplatin and ALIMTA were evaluated in two studies. Study JMAP was a phase 1, dose escalation trial beginning with 500 mg/m2 of ALIMTA and 75 mg/m2 of cisplatin administered once every 21 days to 15 patients with advanced cancers (renal function ranged from 53 to 104 ml/min). ALMITA infusions were 10 minutes in duration, followed 30 minutes later by Cisplatin infusions (2 hrs). Patients were hydrated before and following the cisplatin infusion (1000 and 2000 ml saline, respectively) (Treatment A). A second treatment arm was added in which ALIMTA and cisplatin infusions were separated by 24 hours (Treatment B). Dense sampling for ALIMTA was conducted over 24 hours in arm A, and over 97 hours in treatment arm B. Similar sampling was conducted for cisplatin. ALIMTA plasma concentrations and plasma total platinum were assayed. The results of these studies are listed in Tables 3 and 4 below.

TABLE 3. ALIMTA pharmacokinetics with and without Cisplatin

Parameter	Treatment A 600 mg/m2 (n=4)	Treatment B 500 mg/m2 (n=6)	Treatment B 600 mg/m2 (n=5)
C_{max} (ug/ml)	83.1 (21%)	72.2 (49%)	97.1 (21%)
CL (ml/min/m2)	67.2 (33%)	90.1 (63%)	77.0 (30%)
$T_{1/2}$ (hr)	3.4	2.8	3.1

TABLE 4. Cisplatin (total platinum) pharmacokinetics with and without ALIMTA

Parameter	Treatment A 75 mg/m2 (n=4)	Treatment B 75 mg/m2 (n=7)
C_{max} (ug/ml)	2.58 (17%)	2.62 (49%)
CL (ml/min/m2)	9.31 (65%)	7.12 (29%)
$T_{1/2}$ (hr)	50.4	67.1

No significant interactions between ALIMTA and cisplatin could be observed in this study.

The interaction between cisplatin and ALMITA was also studied as a part of the phase 3 pivotal trial using a population pharmacokinetic approach. Mesothelioma patients were treated with 500 mg/m2 of ALIMTA and 75 mg/m2 of cisplatin administered once every 21 days. ALMITA infusions were 10 minutes in duration, followed 30 minutes later by Cisplatin infusions (2 hrs). The median clearance of ALIMTA was 88.4 ml/min (48.8 ml/min). Inclusion of cisplatin as a covariate to describe ALIMTA clearance had no significant effect. Volume of distribution, however, was reduced significantly by 31%. The clinical significance of this finding is unclear.

Similarly, the cisplatin clearance in this study was measured as 12.3 ml/min (total platinum). This clearance was also unaffected by the inclusion of ALIMTA as a covariate.

Carboplatin

Potential pharmacokinetic interactions between MTA and carboplatin were evaluated in a phase 1 study (JMUA) of 20 patients with pleural mesothelioma. This trial was a phase 1 study of escalating doses of ALIMTA administered as a 10-minute infusion followed 30 minutes later by a 30-minute infusion of carboplatin. Both treatments were repeated every 21-days. Starting ALIMTA doses were 400 mg/m2, and carboplatin was dosed to a target AUC of 4 mg/ml•min. Both ALIMTA and carboplatin were densely sampled (13-14 samples over 24 hours) in the first cycle. Total platinum in plasma was assayed for carboplatin, and the $AUC_{0-\infty}$ for platinum ultrafiltrate was derived using the Ghazal-Aswad method (1996). There was no period when ALIMTA or carboplatin were administered alone. Results from these studies were compared to historical data. The pharmacokinetics of ALIMTA were similar to parameter estimates observed from other phase 1 studies which suggest that carboplatin does not alter ALIMTA in patients with normal renal function, at least in the first cycle of therapy.

TABLE 5. ALIMTA CLEARANCE

Study	ALIMTA Dosage	CL ml/min/m2
JMAU	400	72.8
	500	49.5
	600	45.0
JMAB	40	58.3
JMAA	525	49.3
	600	45.0
	700	45.9
JMAW	500	46.7
	600	47.2

The results for total carboplatin suggest that ALIMTA increases the clearance of carboplatin (see Table 6).

TABLE 6. Carboplatin Pharmacokinetic Parameters

Study	CL (L/hr)	V (L)	$T_{1/2}$ (hrs)
JMAU	8.16	129	15.6
Paraplatin Labeling	4.4	16	3-6
Lee et al 1988	4.3	NA	14.7
Oguri et al 1988	3.7-6.3	NA	1.3-1.7

The sponsor concluded that total carboplatin pharmacokinetics were not reliable because only two sampling times were available to assess terminal elimination. Instead they

calculated free platinum in the plasma ultrafiltrate as a function of the 24-hour total carboplatinum sample using the Ghazal-Aswad method. The resulting platinum ultrafiltrate AUC is 108 μg/ml•min is within the range of values reported in the Ghazal-Aswad report for patients dosed with 400 mg/m2 carboplatin (~ μg/ml•min). The reliability of this approach is questionable, because it depends on the accuracy of a single sample per patient instead of the entire data set. Furthermore, in the Ghazal-Aswad study only 5 patients were dosed with 400 mg/m2 carboplatin, therefore the validation of this approach is not satisfactory.
Overall, the study appears to indicate that ALIMTA pharmacokinetics are not significantly affected by carboplatin, at least not during the first cycle of treatment. ALIMTA elimination may be affected by carboplatin in later cycles of therapy. These data suggest that ALIMTA increases the clearance of carboplatin, which could lead to underexposure of carboplatin. The mechanism of this interaction is unclear, and the interpretation of the study is hampered by lack of an appropriate in-study control.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)

Aspirin

Aspirin has a known effect on the pharmacokinetics of methtrexate, a congener of ALIMTA. A phase 1 study in 24 patients with advanced cancer was conducted to assess the effect of aspirin on the pharmacokinetics of ALIMTA. The patients also had varying degrees of renal impairment (JMAW(2b)). The mean creatinine clearance was 119 ml/min (range: ~ ml/min). The study was a two-way crossover design to facilitate comparison of ALIMTA PK in the presence and absence of aspirin. ALIMTA was administered as a 500 mg/m2 infusion over 10 minutes once every 21 days. Enteric-coated aspirin was administered as 325 mg every 6 hours 2 days before ALIMTA administration (1.3 g/day), and then one tablet was administered one hour prior to ALIMTA administration. Twelve samples for ALIMTA were obtained over 72 hours. Aspirin concentrations were not assessed. The results of the study are listed in Table 7.

TABLE 7. ALIMTA Pharmacokinetics with/without Aspirin

Parameter	ALIMTA alone	ALIMTA+ aspirin
C_{max} (μg/ml)	114 ± 28.1%	111 ± 28.8%
$AUC_{0-\infty}$ (μg•hr/ml	170 ± 33.1%	170 ± 28.1%
CL (ml/min/m2)	53.8 ± 29.2%	52.8 ± 28.5%
$T_{1/2}$ (hrs)	2.73 ± 31.9%	2.85 ± 25.3%

These data suggest that there is no significant effect of aspirin on ALIMTA pharmacokinetics. However, the study does not assess a potential interaction with more prolonged exposure to aspirin, nor does it truly assess the effect that renal impairment may contribute as there were only three patients with mild renal impairment (the remaining patients had normal renal function). Additionally, the dose used in this study (1.3 g/day) is moderate compared to the potential amount of aspirin that might be administered to these patients (2.5 to 3.9 g/day). These latter doses were the doses in which the methotrexate-aspirin interaction was observed. Therefore, interactions at

higher doses may be possible. Another shortcoming of this study is that the effect of ALIMTA on salicyclate excretion was not assessed. Renal excretion of salicyclate may be 30%, and it increases as the dose of aspirin increases. Therefore, the potential for ALIMTA to affect salicyclate excretion should also be addressed.

Ibuprofen

Ibuprofen has a known effect on the pharmacokinetics of methotrexate, a congener of ALIMTA. A phase 1 study in 24 patients with advanced cancer was conducted to assess the effect of ibuprofen on the pharmacokinetics of ALIMTA. The patients also had varying degrees of renal impairment (JMAW(2b)). The mean creatinine clearance was 115 ml/min (range: —— ml/min). The study was a two-way crossover design to facilitate comparison of ALIMTA PK in the presence and absence of aspirin. ALIMTA was administered as a 500 mg/m2 infusion over 10 minutes once every 21 days. Ibuprofen was administered as 400 mg (2-200 mg tablets) every 6 hours for 2 days before ALIMTA administration (1.6 g/day), and then 400 mg was administered one hour prior to ALIMTA administration. Twelve samples for ALIMTA were obtained over 72 hours. Ibuprofen concentrations were not assessed. The results of the study are listed in Table 8.

TABLE 8. ALIMTA Pharmacokinetics with/without Ibuprofen

Parameter	ALIMTA alone	ALIMTA+ ibuprofen
C_{max} (µg/ml)	105 ± 31.3%	121 ± 27.9%
$AUC_{0-\infty}$ (µg•hr/ml	166 ± 23.6%	208 ± 26.3%
CL (ml/min/m2)	52.5 ± 24.4%	43.0 ± 27.2%
$T_{1/2}$ (hrs)	2.9 ± 19.5%	2.9 ± 16.2%

These data indicate that there is a statistically significant increase in ALIMTA AUC (~20%) and C_{max} (~15%), and a significant decrease in CL (~17%). In this case as well, the study does not assess a potential interaction with more prolonged exposure to ibuprofen, nor does it truly assess the effect that renal impairment may contribute as there were only two patients with mild renal impairment (the remaining patients had normal renal function). Additionally, the dose used in this study (1.6 g/day) is moderate compared to the potential amount of ibuprofen that might be administered to these patients. Previous studies have shown that ibuprofen doses of 2.4 to 3.6 g/day induced a 40% reduction in total and renal clearance of methotrexate (Tracy 1992). Therefore, interactions at higher doses may be possible.

5-Fluorouracil (5-FU)

The effect of ALIMTA on 5-FU (and vice versa) was to be studied in a phase 1 study of this drug combination in patients with locally advanced or metastatic cancer (JMAR). However, the third amendment to the protocol removed the pharmacokinetic objective from the study, and data was collected for only 2 patients. Consequently, potential drug-drug interactions for this combination have not been examined.

Vinorelbine

The effect of ALIMTA on vinorelbine (and vice versa) was to be studied in a phase 3 study of this drug combination in patients with locally advanced or metastatic non-small cell lung cancer (JMBQ). However, the study was terminated prematurely due to low enrollment, and data was collected for only 3 patients. Consequently, potential drug-drug interactions for this combination have not been examined.

E. General Biopharmaceutics

The BCS, bioavailability and bioequivalence issues relevant to per oral formulations do not apply to ALIMTA as it is a reconstituted lyophilized or aqueous solution for intravenous administration.

F. Analytical Section

The sponsor submitted method validation studies for MTA, cisplatin, carboplatin, and folic acid.

MTA (ALIMTA)

Several assays were submitted for MTA quantification. Overall, there were two basic assays, one based on LC/MS/MS and the second was —. The — assay consisted of three parts.

Method — was the LC/MS/MS method that assayed MTA concentrations from — —) **ng/ml** in human plasma. No interfering peaks were observed at the retention time for MTA. The limit of quantification (LOQ) was —ng/ml, and the accuracy and precision measurements were below —%. The accuracy of the QC samples were also less than —% for the room temperature (up to 24 hours) and autosampler — stability tests. The precision of the low QC sample (—ng/ml) following three freeze-thaw cycles was slightly high (—%), but this is not likely problematic. The accuracy and precision of the high QC samples was less than —%.

Method — } was the LC/MS/MS method that assayed MTA concentrations from — **ng/ml** in human plasma. No interference peaks were observed at the retention time for MTA. The limit of quantification (LOQ) was — ıg/ml, and the accuracy and precision measurements were below —%. The accuracy of the QC samples were also less than —% for the room temperature and autosampler stability tests. The accuracy and precision of the low and high QC samples (— ng/ml) following three freeze-thaw cycles was —% or less.

Method — was the LC/MS/MS method that assayed MTA concentrations from — **ng/ml** in human urine. No interference peaks were observed at the retention time for MTA. The limit of quantification (LOQ) was —) ng/ml, and the accuracy and precision measurements were below —%. The precision of the low QC sample (—) ng/ml) at 4 hours was slightly high (— %) and the accuracy at 24 hours was — % at room temperature. However, the remaining measurements of accuracy and

precision at 4 and 24 hours were less than — , for the room temperature and autosampler stability tests. The accuracy and precision of the low and high QC samples (—
— ng/ml) following three freeze-thaw cycles was — %.

Method —— Feb94 was a HPLC method with ultraviolet (UV) detection. Human plasma concentrations of MTA were measured over ranges of ——
—— The accuracy and precision for each concentration range was less than %. No interference was detected at the retention time of MTA or its internal standard. The limit of quantification was — ng/ml, where accuracy and precision were less than —%. No freeze-thaw, room temperature or autosampler stability data was reported.

Method —— -01Jul94 was a HPLC method with ultraviolet (UV) detection. Human urine concentrations of MTA were measured over ranges of ——
— . The accuracy and precision for each concentration range was — % or less. Some interference was detected at the retention time of MTA. The signal to noise ratio for the interference was equivalent to — ug/ml MTA. The sponsor set the limit of quantification as— ıg/ml, however, according to the Bioanalytical Method Validation Guidance, the LOQ should be set at 5 x higher than the interference, or— ıg/ml. The sponsor reported that MTA urine concentrations of —— ug/ml were stable when frozen at —— °C. However no data was provided nor was the timeframe defined. The sponsor also reported that MTA degraded after an unspecified period at room temperature, and incorporated storage of samples on ice into the method. Again no data was reported.

MTA alone was assayed in these studies because greater than 90% of radiolabeled MTA was excreted in the urine as unchanged parent. Similar observations were made for MTA in humans. The main metabolite produced is M1 (LY338979) which accounted for less than 5% of the dose based on the relative ion intensity (ADME report 15). Total plasma concentrations of MTA were assessed, as plasma protein binding is not considered very high (80%; ADME reports 14 and 21).

No long term stability data for MTA was provided in any of the studies. Therefore, it is unclear how long the samples can be reliably stored. No formal cross-validation studies were performed to determine whether one method was biased relative to the other. However, the effect of the assay was a covariate that was explored in the population PK analysis of MTA; no effect was detected, suggesting that both methods provide accurate unbiased MTA quantification.

CISPLATIN

The sponsor submitted two method validation studies for cisplatin analysis.

Method — is an atomic absorption spectrophotometric assay. Human plasma concentrations of platinum (Pt), derived from Cisplatin, were measured over the concentration range of —— ng/ml. The LOQ was — ng/ml. No interference

with Pt was detected in blank plasma (ultrafiltrate). No interference in the quantification of Pt by MTA at concentrations of [redacted] ng/ml was detected. Accuracy and precision were less than [redacted]% at all concentrations. Low and high concentration samples were within [redacted] of starting concentrations stable after 2 freeze-thaw cycles.

Method [redacted] (22-Feb-99) is an atomic absorption spectrophotometric assay. Human plasma concentrations of platinum (Pt), derived from Cisplatin, were measured over the concentration range of [redacted] ng/ml. The LOQ was [redacted] ng/ml. No interference with Pt was detected in blank plasma. No interference in the quantification of Pt by MTA at concentrations of [redacted] ng/ml was detected. Accuracy and precision were less than [redacted]% at all concentrations. Low and high concentration samples were within [redacted] % of starting concentrations stable after [redacted] freeze-thaw cycles.

CARBOPLATIN

Method [redacted] (Dec 2000) is an atomic absorption spectrophotometric assay. Human plasma concentrations of platinum (Pt), derived from Carboplatin, were measured over the concentration range of [redacted] ng/ml. The LOQ was [redacted] ng/ml. No interference with Pt was detected in blank plasma. Accuracy was within [redacted]% at all concentrations. Precision was between [redacted] %. Samples were reported to be stable at [redacted] days. Samples were reported to be stable for [redacted] on the benchtop, and following [redacted] freeze-thaw cycles (data not reported).

All of the platinum assays reported were based on total platinum in plasma. This approach is acceptable for Carboplatin, which largely remains unchanged until it is excreted renally. However, Cisplatin rapidly undergoes hydrolysis upon administration and gives rise to a number of protein platinum adducts. Previous pharmacokinetic studies have quantified total platinum in plasma ultrafiltrate, based on the belief that this is the only (remaining) platinum species that can mediate an effect. Therefore, it is unclear whether changes total platinum in plasma reflect changes in the biologically active moiety.

FOLIC ACID

Method [redacted] is radioimmunoassay based on an anti-rabbit IgG raised against folic acid. Human plasma concentrations of folic acid were measured over the concentration range of [redacted] ng/ml. The LOQ was [redacted] ng/ml. Cross-reactivity screening indicate that the assay was approximately ten-fold more selective for folic acid than its metabolites tetrahydrofolate and tetrahydrofolic acid. The assay was [redacted] more selective for folic acid than for MTA. Accuracy and precision were within [redacted]% at all concentrations. Samples were reported to be stable at [redacted] (no data). Samples were reported to be stable for [redacted] on the benchtop, and following 3 freeze-thaw cycles (data not reported).

JMCH: ALIMTA plus Cisplatin—RF in at least 10 cycles

References

Lee EJ, Egorin MJ, Van Echo DA et al Phase 1 and Pharmacokinetic Trial of Carboplatin in Refractory Adult Leukemia. J Natl Cancer Inst 1988 80:131-135.

Oguri S, Sakakibara, Mase H, Shimizu T. et al Clinical Pharmacokinetics of Carboplatin. J Clin Pharmacol 1988 28:208-215.

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information

PPK
Studies JMAC, JMAD, JMAD, JMAH, JMAI, JMAJ, JMAK, JMAM, JMAL, JMBR

Table POPK.6.1. Cancer Types for Studies Included in the Population Pharmacokinetic Analyses

Study Code	Cancer Type
H3E-MC-JMAC	Metastatic Colorectal Cancer
H3E-MC-JMAD	Metastatic Pancreatic Cancer
H3E-MC-JMAG	Locally/Regionally Recurrent or Metastatic Breast Cancer
H3E-MC-JMAH	Esophagus Cancer
H3E-MC-JMAI	Metastatic Renal Cancer
H3E-MC-JMAJ	Locally Advanced or Metastatic Head and Neck Cancer
H3E-MC-JMAK	Advanced Bladder Cancer
H3E-MC-JMAL	Non-Small Cell Lung Cancer
H3E-MC-JMAM	Cervical Cancer
H3E-MC-JMBR	Non-Small Cell Lung Cancer (in patients who have failed previous chemotherapy)

3 phase 1 studies.
JMAA: 10-min infusion q1wk every 21 days.
JMAB: 10-min infusion Q1wk x 3, then 3wks of rest
BP001: 10-min infusion daily for 5 days, then 16 days of rest; kinetics different in this study.

Objectives
- Overall disposition of mTA
- Identification of covariates
- Characterization of between and within patient variability.

V: 15 L
T1/2 2-5 hrs. (525 to 700 mg/m2)

Methods

Formulation: 40 ml aqueous solution 200 or 1000 mg
Dose: initial dose was 500-600 mg/m2 every 21-days

PPK: 287 patients, 1596 samples, 159 men, 128 women from phase 2 studies
Index dataset: JMAC, JMAD, JMAG, JMAI, JMAJ, JMAK, JMAM
Validation dataset: JMAL, JMBR

.Samples

Sparse sampling during cycles 1and 2.

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

Table POPK.9.1. Summary of Baseline Age, Body Surface Area, Weight and Cockcroft-Gault Creatinine Clearance for LY231514-Treated Patients in the Index and Validation Datasets

	Age * (years)	BSA * (m²)	Weight * (kg)	CGCL * (mL/min)
Index 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)
Validation Dataset (n=78)				
Range	36.6 – 80.2	1.28 – 2.35	36.0 - 127	40.7 - 162
Mean (CV as %)	60.6 (16)	1.78 (12)	69.3 (23)	92.8 (27)

* Baseline patient characteristics

Abbreviations: BSA = Body Surface Area; CGCL = Cockcroft-Gault creatinine clearance.

Table POPK.9.3. Summary of Ethnic Origin for LY231514-Treated Patients in the Index and Validation Datasets

Ethnic Group	Index Dataset	Validation Dataset
Caucasian	160 (77%)	59 (76%)
African Descent	35 (17%)	3 (4%)
Asian	2 (1%)	3 (4%)
Hispanic	2 (1%)	0
Other [a]	10 (5%)	13 (17%)
N [b]	209	78

[a] Undefined ethnic origin.

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

Analysis
HPLC/UV: JMAC, JMAD, JMAG, JMAH

LC/MS/MS: JMAI, JMAJ, JMAK, JMAL, JMAM and JMBR

Cockcroft-Gault CLcr

CGCL = [(140-age(years))x weight(kg))]/(72xserum creatinine concentration (mg/dL)
Multiply by 0.85 for females.

Lean Body Mass
LBM(kg)= [0.3281 x weight (kg)] + [0.33929 x height(cm)]-29.5336

LBM(kg)= [0.29569 x weight (kg)] + [0.41813 x height(cm)]-43.2933 for females

CLBM = [140-age (years) x LBM]

Modeling

Base model:
Two compartment model based on previous experience and index set data. Once defined, covariates added to model. Used JMAA, JMAB, BP001. ADVAN 3

Missing Data
Datasest with missing dates or times were excluded from analysis. Patient demographic data were imputed if missing at subsequent visits.
Outliers: points deleted if physiologically implausible.

Tried FO, FOCE and FOCE/I
Tried additive, proportional and combined error models for variability and residual error.

Covariates: Effect of

$P = \theta 1 + \theta 2 x COV$
$P = \theta 1 \times (1 + \theta 2 x COV)$
$P = \theta 1 \times COV^{\theta 2}$

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,
Aspartate Transaminase (AST)	Methylmalonic Acid, Cystathionine, and
Body Mass Index	Methylcitrate I and II)
Body Surface Area	Gender
Body Weight	Smoking status
Creatinine Clearance (estimated by Cockcroft-Gault formula using age, weight, and serum creatinine)	Treatment cycle (cycle =1 versus cycle >1)
Creatinine Clearance (estimated by Cockcroft-Gault formula using age, lean body mass, and serum creatinine)	
Dose	
Serum Creatinine	
Total Bilirubin	
Total Protein	

Covariates were selected sequentially, if they reduced MOF by 3.841 points.

Final model

Some covariates were confounded. CGCL had a large effect because MTA is renally excreted. All covariates tested with CGCL. Covariates identified were then sequentially removed to evaluate their impact. Covariates were retained if removal changed MOF by 10.828

Sensitivity Analysis

Parameters were fixed at population mean +/- 5 to 40% and estimating all other parameters.

Leverage analysis based on 10 subsets

Index set data used to data from validation set. Used index set population mean to assess valdiation set. Calculated MPE, MSPE and MRE (bias)

Final Model

$CL = TVCL + \theta1 \bullet CGCL/92.6$

$V1 = TVV1 \bullet BSA^{\theta2}$

Table 1 (continued) Covariate Identification (Part I). Covariates Individually on Each Pharmacokinetic Parameter

Key Runs	Run	Notes	MOF	ΔMOF rel to base	ΔMOF >3.841	Success
	023	Effect of ALT on V2 proportional model (ALT/median)	19372.94	-0.477		SUCCESSFUL
	027	Effect of ALT on V2 linear model (ALT/median)	19372.939	-0.478		SUCCESSFUL
	029	Effect of ALT on V2 power model (multi) (ALT)	19373.406	-0.011		SUCCESSFUL
	003	Effect of AST on CL proportional model (AST/median)	19373.287	-0.130		SUCCESSFUL
	007	Effect of AST on CL linear model (AST/median)	19373.287	-0.130		SUCCESSFUL
	009	Effect of AST on CL power model (multi) (AST)	19370.091	-3.326		SUCCESSFUL
	013	Effect of AST on V1 proportional model (AST/median)	19372.719	-0.698		SUCCESSFUL
	017	Effect of AST on V1 linear model (AST/median)	19372.72	-0.697		SUCCESSFUL
*	019	Effect of AST on V1 power model (multi) (AST)	19369.095	-4.322	*	SUCCESSFUL
	023	Effect of AST on V2 proportional model (AST/median)	19373.377	-0.040		SUCCESSFUL
	027	Effect of AST on V2 linear model (AST/median)	19373.374	-0.043		SUCCESSFUL
	029	Effect of AST on V2 power model (multi) (AST)	19372.341	-1.076		SUCCESSFUL
	003	Effect of BMI on CL proportional model (BMI/median)	19372.84	-0.577		SUCCESSFUL
	007	Effect of BMI on CL linear model (BMI/median)	19372.906	-0.511		SUCCESSFUL
	009	Effect of BMI on CL power model (multi) (BMI)	19373.143	-0.274		SUCCESSFUL
	013	Effect of BMI on V1 proportional model (BMI/median)	19368.096	-5.321	*	SUCCESSFUL
*	017	Effect of BMI on V1 linear model (BMI/median)	19368.096	-5.321	*	SUCCESSFUL
	019	Effect of BMI on V1 power model (multi) (BMI)	19368.858	-4.559	*	SUCCESSFUL
	023	Effect of BMI on V2 proportional model (BMI/median)	19368.933	-4.484	*	SUCCESSFUL
*	027	Effect of BMI on V2 linear model (BMI/median)	19368.934	-4.483	*	SUCCESSFUL
	029	Effect of BMI on V2 power model (multi) (BMI)	19369.487	-3.930	*	SUCCESSFUL
	003	Effect of BSAV on CL proportional model (BSAV/median)	19369.683	-3.734		SUCCESSFUL
	007	Effect of BSAV on CL linear model (BSAV/median)	19369.997	-3.420		SUCCESSFUL
*	009	Effect of BSAV on CL power model (multi) (BSAV)	19369.465	-3.952	*	SUCCESSFUL
	013	Effect of BSAV on V1 proportional model (BSAV/median)	19332.013	-41.404	*	SUCCESSFUL
	017	Effect of BSAV on V1 linear model (BSAV/median)	19331.629	-41.788	*	SUCCESSFUL ESTIMATE OF THETA NEAR THE BOUNDARY. PROBABLY UNINTERPRETABLE

Table 1 (continued) Covariate Identification (Part I), Covariates Individually on Each Pharmacokinetic Parameter

Key Runs	Run	Notes	MOF	ΔMOF rel to base	ΔMOF >3.841	Success
*	019	Effect of BSAV on V1 power model (multi) (BSAV)	19331.274	-42.243	*	SUCCESSFUL
	023	Effect of BSAV on V2 proportional model (BSAV/median)	19369.079	-4.338	*	SUCCESSFUL
	027	Effect of BSAV on V2 linear model (BSAV/median)	19369.078	-4.339	*	SUCCESSFUL
*	029	Effect of BSAV on V2 power model (multi) (BSAV)	19369.396	-4.021	*	SUCCESSFUL
	003	Effect of CLBM on CL proportional model (CLBM/median)	19265.818	-107.599	*	SUCCESSFUL
*	007	Effect of CLBM on CL linear model (CLBM/median)	19265.787	-107.630	*	SUCCESSFUL
	009	Effect of CLBM on CL power model (multi) (CLBM)	19262.253	-111.164	*	SUCCESSFUL
	013	Effect of CLBM on V1 proportional model (CLBM/median)	19366.388	-7.029	*	SUCCESSFUL
*	017	Effect of CLBM on V1 linear model (CLBM/median)	19366.387	-7.030	*	SUCCESSFUL
	019	Effect of CLBM on V1 power model (multi) (CLBM)	19364.692	-8.725	*	SUCCESSFUL
	023	Effect of CLBM on V2 proportional model (CLBM/median)	19372.272	-1.145		SUCCESSFUL
	027	Effect of CLBM on V2 linear model (CLBM/median)	19372.272	-1.145		SUCCESSFUL
	029	Effect of CLBM on V2 power model (multi) (CLBM)	19371.016	-2.401		SUCCESSFUL
	003	Effect of CGCL on CL proportional model (CGCL/median)	19278.338	-95.079	*	SUCCESSFUL
*	007	Effect of CGCL on CL linear model (CGCL/median)	19278.352	-95.065	*	SUCCESSFUL
	009	Effect of CGCL on CL power model (multi) (CGCL)	19272.774	-100.643	*	SUCCESSFUL
	013	Effect of CGCL on V1 proportional model (CGCL/median)	19372.756	-0.661		SUCCESSFUL
	017	Effect of CGCL on V1 linear model (CGCL/median)	19372.756	-0.661		SUCCESSFUL
	019	Effect of CGCL on V1 power model (multi) (CGCL)	19371.278	-2.139		SUCCESSFUL
	023	Effect of CGCL on V2 proportional model (CGCL/median)	19373.354	-0.063		SUCCESSFUL
	027	Effect of CGCL on V2 linear model (CGCL/median)	19373.354	-0.063		SUCCESSFUL
	029	Effect of CGCL on V2 power model (multi) (CGCL)	19373.076	-0.341		SUCCESSFUL
	003	Effect of DDI on CL proportional model (DDI/median)	19372.890	-0.527		SUCCESSFUL
	007	Effect of DDI on CL linear model (DDI/median)	19372.890	-0.527		SUCCESSFUL
	009	Effect of DDI on CL power model (multi) (DDI)	19373.344	-0.073		SUCCESSFUL
	013	Effect of DDI on V1 proportional model (DDI/median)	19369.718	-3.699		SUCCESSFUL
	017	Effect of DDI on V1 linear model (DDI/median)	19369.704	-3.713		SUCCESSFUL
	019	Effect of DDI on V1 power model (multi) (DDI)	19370.649	-2.768		SUCCESSFUL
	023	Effect of DDI on V2 proportional model (DDI/median)	19372.842	-0.575		SUCCESSFUL

Table 1 (continued) Covariate Identification (Part I), Covariates Individually on Each Pharmacokinetic Parameter

Key Runs	Run	Notes	MOF	ΔMOF rel to base	ΔMOF >3.841	Success
	029	Effect of DDI on V2 power model (multi) (DDI)	19607.867	.		MINIMIZATION TERMINATED DUE TO ROUNDING ERRORS
*	001	Effect of GEN on CL	19367.593	-5.824	*	SUCCESSFUL
*	002	Effect of GEN on V1	19332.457	-40.960	*	SUCCESSFUL
	003	Effect of GEN on V2	19371.754	-1.663		SUCCESSFUL
	001	Effect of ORIG on CL (Cauc v. others)	19372.08	-1.337		SUCCESSFUL
	002	Effect of ORIG on CL (AfAm v. others)	19372.534	-0.883		SUCCESSFUL
	003	Effect of ORIG on CL (Other v. specified)	19372.608	-0.809		SUCCESSFUL
	004	Effect of ORIG on CL (Hisp v. others)	19373.321	-0.096		SUCCESSFUL
	005	Effect of ORIG on CL (EastAs v. others)	19373.217	-0.200		SUCCESSFUL
	006	Effect of ORIG on CL (Asian v. others)	19373.41	-0.007		SUCCESSFUL
	007	Effect of ORIG on CL (all groups separately)	19371.284	-2.133		SUCCESSFUL
	008	Effect of ORIG on CL (Cauc v. Af v. Other)	19372.081	-1.336		SUCCESSFUL
	009	Effect of ORIG on V1 (Cauc v. others)	19363.272	-10.145	*	SUCCESSFUL
	010	Effect of ORIG on V1 (AfAm v. others)	19369.465	-3.952	*	SUCCESSFUL
	011	Effect of ORIG on V1 (Other v. specified)	19365.722	-7.695	*	SUCCESSFUL
	012	Effect of ORIG on V1 (Hisp v. others)	19373.338	-0.079		SUCCESSFUL
	013	Effect of ORIG on V1 (EastAs v. others)	19373.244	-0.173		SUCCESSFUL
	014	Effect of ORIG on V1 (Asian v. others)	19373.524	0.107		SUCCESSFUL
	015	Effect of ORIG on V1 (all groups separately)	19359.829	-13.588	*	SUCCESSFUL
	016	Effect of ORIG on V1 (Cauc v. Af v. Other)	19362.357	-11.060	*	SUCCESSFUL
	017	Effect of ORIG on V2 (Cauc v. others)	19369.447	-3.970	*	SUCCESSFUL
	018	Effect of ORIG on V2 (AfAm v. others)	19365.161	-8.256	*	SUCCESSFUL
	019	Effect of ORIG on V2 (Other v. specified)	19373.358	-0.059		SUCCESSFUL
	020	Effect of ORIG on V2 (Hisp v. others)	19369.090	-4.327	*	SUCCESSFUL
	021	Effect of ORIG on V2 (EastAs v. others)	19373.072	-0.345		SUCCESSFUL
	022	Effect of ORIG on V2 (Asian v. others)	19373.405	-0.012		MINIMIZATION TERMINATED DUE TO ROUNDING ERRORS

Table 1 (continued) Covariate Identification (Part I). Covariates Individually on Each Pharmacokinetic Parameter

Key Runs	Run	Notes	MOF	ΔMOF rel to base	ΔMOF >3.841	Success
	023	Effect of ORIG on V2 (all groups separately)	19356.238	-14.179	*	MINIMIZATION TERMINATED DUE TO ROUNDING ERRORS
	024	Effect of ORIG on V2 (Cauc v. Af v. Other)	19364.697	-8.720	*	SUCCESSFUL COVARIANCE STEP ABORTED
	024	Effect of ORIG on V2 (Cauc v. Af v. Other)	19364.698	-8.719	*	SUCCESSFUL
*	102	Effect of ORIG on V1 (Cauc v. African American)	19362.349	-11.068	*	SUCCESSFUL
*	103	Effect of ORIG on V2 (Cauc v. African American)	19365.628	-7.789	*	SUCCESSFUL
	003	Effect of CR on CL proportional model (CR/median)	19314.269	-59.148	*	SUCCESSFUL
*	007	Effect of CR on CL linear model (CR/median)	19314.269	-59.148	*	SUCCESSFUL
	009	Effect of CR on CL power model (multi) (CR)	19319.123	-54.294	*	SUCCESSFUL
	013	Effect of CR on V1 proportional model (CR/median)	19324.339	-49.078	*	SUCCESSFUL
*	017	Effect of CR on V1 linear model (CR/median)	19324.339	-49.078	*	SUCCESSFUL
	019	Effect of CR on V1 power model (multi) (CR)	19326.065	-47.352	*	SUCCESSFUL
	023	Effect of CR on V2 proportional model (CR/median)	19362.623	-10.794	*	SUCCESSFUL
*	027	Effect of CR on V2 linear model (CR/median)	19362.623	-10.794	*	SUCCESSFUL
	029	Effect of CR on V2 power model (multi) (CR)	19364.514	-8.903	*	SUCCESSFUL
	001	Effect of SMKI: on CL	19372.508	-0.909		SUCCESSFUL
	002	Effect of SMKI: on V1	19372.7	-0.717		SUCCESSFUL
	003	Effect of SMKI: on V2	19373.383	-0.034		SUCCESSFUL
	003	Effect of TBI on CL proportional model (TBI/median)	19372.894	-0.523		SUCCESSFUL
	007	Effect of TBI on CL linear model (TBI/median)	19372.893	-0.524		SUCCESSFUL
	009	Effect of TBI on CL power model (multi) (TBI)	19373.41	-0.007		SUCCESSFUL
	013	Effect of TBI on V1 proportional model (TBI/median)	19373.008	-0.409		SUCCESSFUL
	017	Effect of TBI on V1 linear model (TBI/median)	19373.008	-0.409		SUCCESSFUL
	019	Effect of TBI on V1 power model (multi) (TBI)	19373.39	-0.027		SUCCESSFUL
	023	Effect of TBI on V2 proportional model (TBI/median)	19370.837	-2.580		SUCCESSFUL
	027	Effect of TBI on V2 linear model (TBI/median)	19370.806	-2.611		SUCCESSFUL
	029	Effect of TBI on V2 power model (multi) (TBI)	19370.444	-2.973		SUCCESSFUL
	003	Effect of TPRO on CL proportional model (TPRO/median)	19360.601	-12.816	*	SUCCESSFUL

Table 1 (concluded) Covariate Identification (Part I). Covariates Individually on Each Pharmacokinetic Parameter

Key Runs	Run	Notes	MOF	ΔMOF rel to base	ΔMOF >3.841	Success
*	007	Effect of TPRO on CL linear model (TPRO/median)	19360.602	-12.815	*	SUCCESSFUL
	009	Effect of TPRO on CL power model (multi) (TPRO)	19362.311	-11.106	*	SUCCESSFUL
	013	Effect of TPRO on V1 proportional model (TPRO/median)	19373.132	-0.285		SUCCESSFUL
	017	Effect of TPRO on V1 linear model (TPRO/median)	19373.132	-0.285		SUCCESSFUL
	019	Effect of TPRO on V1 power model (multi) (TPRO)	19373.446	0.029		SUCCESSFUL
	023	Effect of TPRO on V2 proportional model (TPRO/median)	19373.418	0.001		SUCCESSFUL
	027	Effect of TPRO on V2 linear model (TPRO/median)	19373.418	0.001		SUCCESSFUL
	029	Effect of TPRO on V2 power model (multi) (TPRO)	19373.325	-0.092		SUCCESSFUL
	003	Effect of WTV on CL proportional model (WTV/median)	19372.429	-0.988		SUCCESSFUL
	007	Effect of WTV on CL linear model (WTV/median)	19372.514	-0.903		SUCCESSFUL
	009	Effect of WTV on CL power model (multi) (WTV)	19372.142	-1.275		SUCCESSFUL
	013	Effect of WTV on V1 proportional model (WTV/median)	19343.287	-30.130	*	SUCCESSFUL
*	017	Effect of WTV on V1 linear model (WTV/median)	19343.254	-30.163	*	SUCCESSFUL
	019	Effect of WTV on V1 power model (multi) (WTV)	19367.019	-6.398	*	SUCCESSFUL
	023	Effect of WTV on V2 proportional model (WTV/median)	19367.965	-5.452	*	SUCCESSFUL
*	027	Effect of WTV on V2 linear model (WTV/median)	19367.966	-5.451	*	SUCCESSFUL
	029	Effect of WTV on V2 power model (multi) (WTV)	19368.792	-4.625	*	SUCCESSFUL

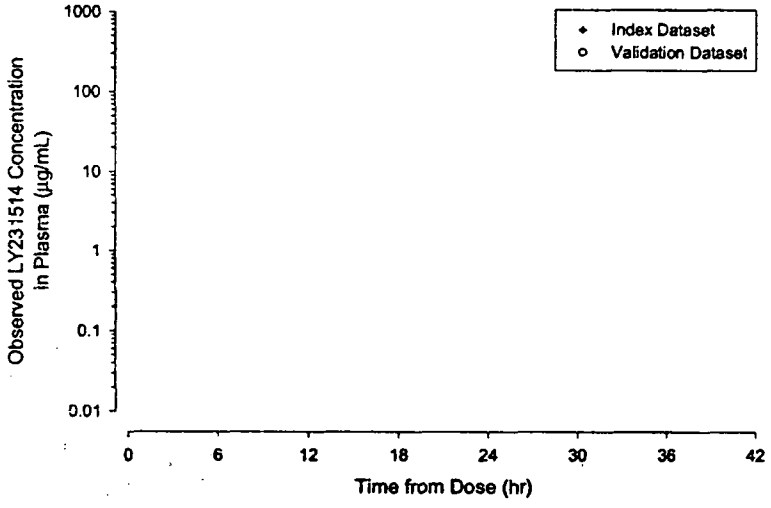


Figure POPK.9.3. Observed LY231514 Concentrations in Plasma Versus Time from Start of Infusion (all doses)

Goodness-of-fit assessment for the final model

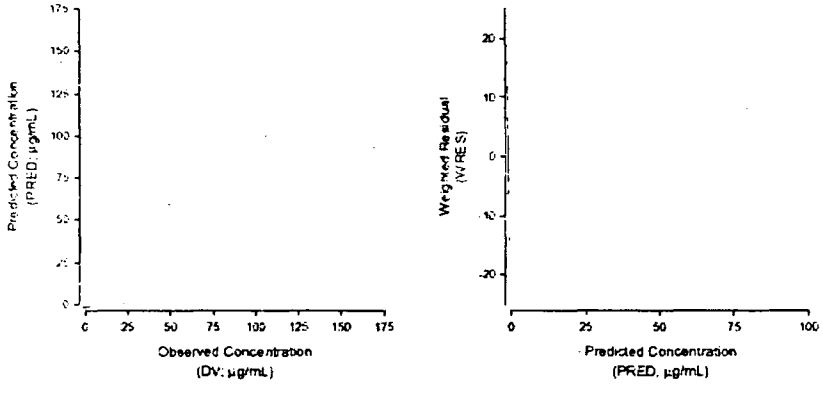
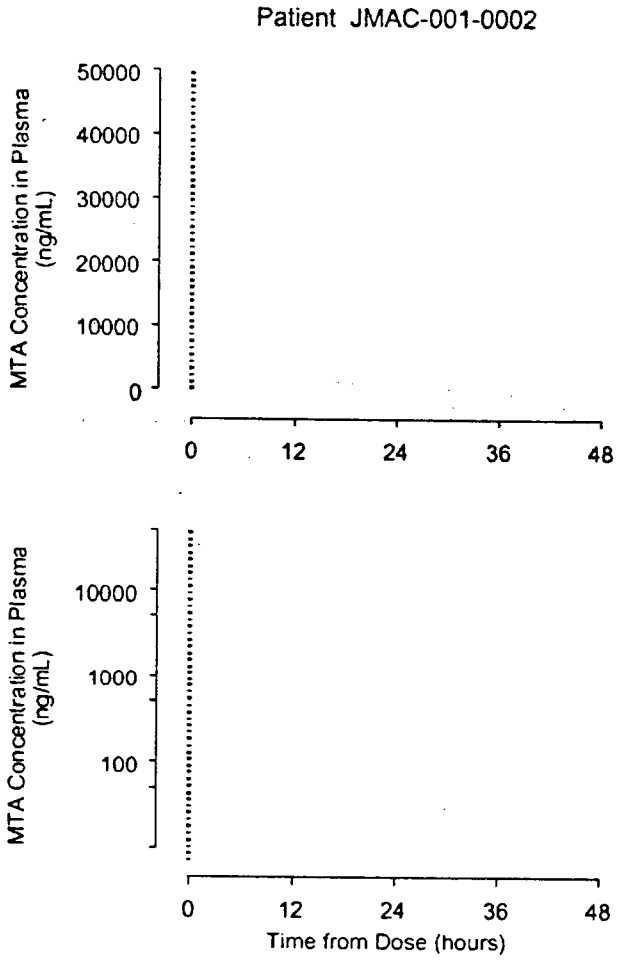


Figure POPK.9.7. Predicted Concentrations and Weighted Residuals for Final LY231514 Model

Individual Patient Concentration vs time.


Patient JMAC-001-0002
MTA Concentration in Plasma (ng/mL)
50000
40000
30000
20000
10000
0
0
12
24
36
48
MTA Concentration in Plasma (ng/mL)
10000
1000
100
0
12
24
36
48
Time from Dose (hours)

Base model

Table POPK.9.5.a. Pharmacokinetic Parameters in Base Population Model for LY231514

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability (%SEE)
Clearance		
Parameter for CL (mL/min)	91.6 (2.36)	25.8% (11.3)
Central Volume of Distribution		
Parameter for V_1 (L)	12.9 (3.86)	24.0% (23.7)
Intercompartmental Clearance		
Parameter for Q (mL/min)	14.4 (17.9)	—
Peripheral Volume of Distribution		
Parameter for V_2 (L)	3.38 (11.0)	26.0% (22.1)
Residual Error (proportional)	28.2% (9.26)	

Abbreviations: SEE = standard error of the estimate

Method: FOCE with interaction

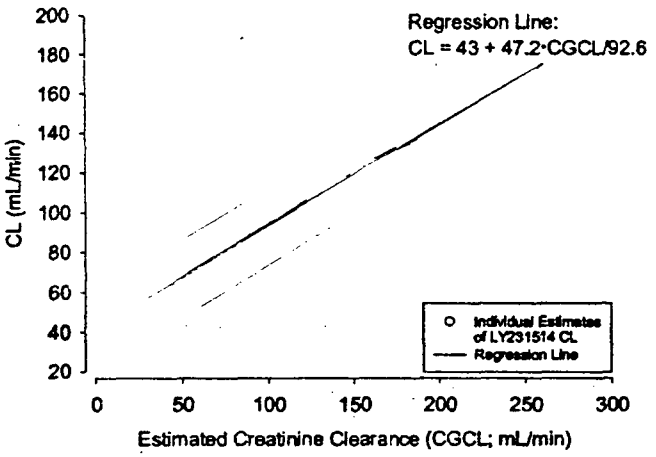
Table POPK.9.5.b. Pharmacokinetic Parameters in Base Population Model for LY231514 (BSA-normalized model parameters)

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability (%SEE)
Clearance		
Parameter for CL (mL/min/m^2)	52.4 (2.31)	26.0% (11.6)
Central Volume of Distribution		
Parameter for V_1 (L/m^2)	7.33 (3.49)	19.4% (27.7)
Intercompartmental Clearance		
Parameter for Q (mL/min/m^2)	8.70 (15.6)	—
Peripheral Volume of Distribution		
Parameter for V_2 (L/m^2)	2.00 (9.5)	26.2% (19.5)
Residual Error (proportional)	27.7% (9.16)	

Abbreviations: SEE = standard error of the estimate

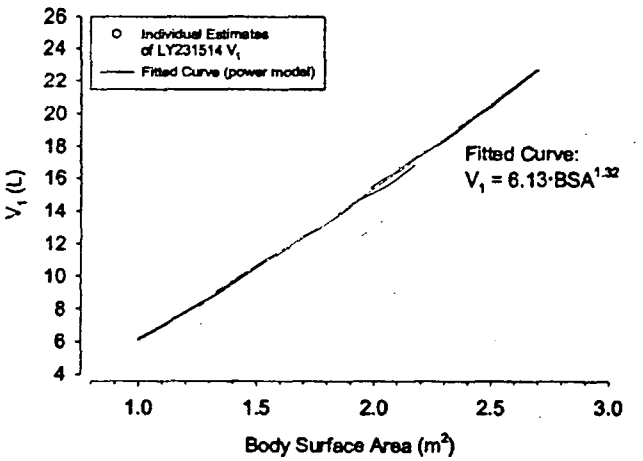
Method: FOCE with interaction

Effect of different assays tested. No effect on residual error or MTA CL therefore, concluded that no sig diff between the two assays.



9.4. Relationship between creatinine clearance and LY231514 CL

63% decrease in CGCL reduces MTA CL by 32%.



9.5. Relationship between body surface area and LY231514 V_1

BSA affected V1, which is expected to affect Cmax, but not t1/2 or AUC.

Folate deficiency
5 patients had a single folate defiecient cycle. Compared to 178 treatment cycles, CL decreased by 33% (change in MOF of 28.7). **This effect was not retained in the model.** Defined as homocysteine > 13.9 μM, cystationine. 342 nM, and methylmalonic acid> 73 but <271 nM.

Gender, Age, race: no effect on MTA
Gender on CL, V1 and V2 MOF <10.8
Age MOF <3.841
Ethnicity MOF <10.828. Only 5 Asian and 2 Hispanic patients. 11% African American, 76% Caucasian.

Smoking, alcohol and dose did not appear to affect MTA PK.
CL decreased by 4% and V1 increased by 10% in later cycles of therapy. Although significant changes, not considered clinically important.

Final Model

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] $CL = TVCL + \Theta_1 \bullet CGCL/92.6$ where 92.6 is the median baseline CGCL.
[b] $V_1 = TVV1 \bullet BSA^{\Theta 2}$
Abbreviations: SEE = standard error of the estimate.
Method: FOCE with interaction

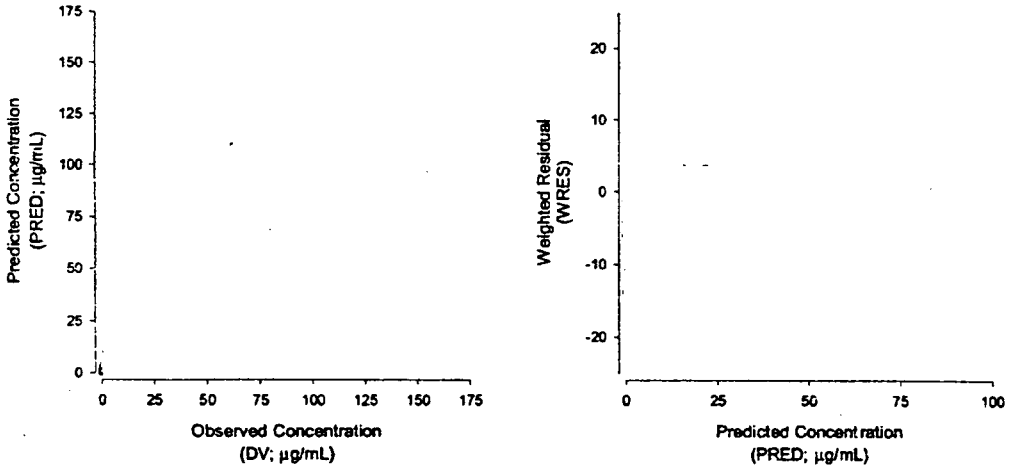


Figure POPK.9.7. Predicted Concentrations and Weighted Residuals for Final LY231514 Model

Higher concentrations not well predicted by model. Sponsor speculated that samples may have been taken from infusion arm.

Sensitivity analysis suggests that the final model was appropriate, based in 95% CI for sensitivity that are often narrower than actual measurements based on error of the estimates.

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

		Calculated [a]		Parameter Sensitivity	
	Parameter	95% Confidence Interval		95% Confidence Interval	
Parameter	Estimate	Lower	Upper	Lower	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.

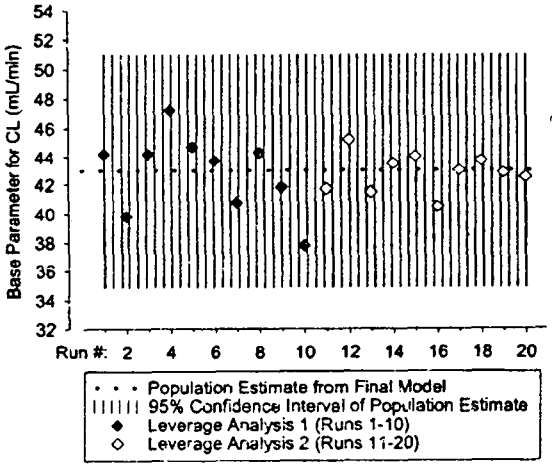
Abbreviations: CL = clearance; V_1 = central volume of distribution; Q = intercompartmental clearance; V_2 = peripheral volume of distribution; CGCL = creatinine clearance; BSA = body surface area; Pt = patient; Var = variability.

Leverage

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

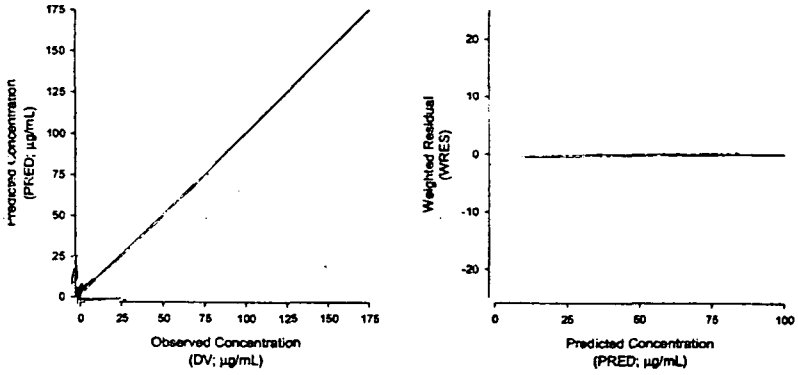
		Parameter Sensitivity 95% Conf Interval		Leverage Analysis Range of Values	
Parameter	Estimate	Lower	Upper	Analysis I	Analysis II
Base parameter for CL (mL/min)	43.0	34.9	51.0	37.8 - 47.2	40.5 - 45.2
Base parameter for V_1 (L)	6.13	5.14	7.34	5.70 - 6.40	5.86 - 6.51
Q (mL/min)	14.5	11.5	18.0	12.7 - 16.0	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; V_2 = peripheral volume of distribution; CGCL = creatinine clearance; BSA = body surface area; Pt = patient; Var = variability.



8. **Estimates of the Base Parameter for CL from Leverage Analyses**

Predictive ability: validation data used with final model and population means from index data set.



igure POPK.9.9. Predicted Concentrations and Weighted Residuals for Final LY231514 Model Applied to Validation Dataset

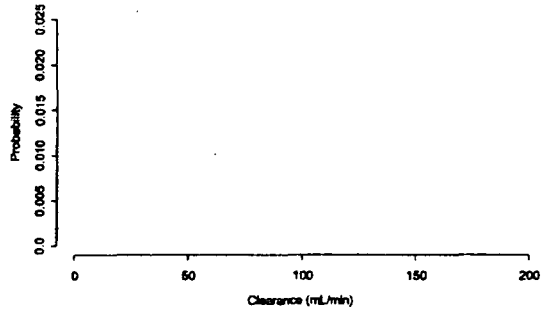
Open circles represent the validation dataset; crosses represent the index dataset.

Table POPK.9.9. Comparison of Prediction Errors: Index and Validation Datasets

	Index Dataset	Validation Dataset
MPE	1.33	1.44
MSPE	140	198
MRE	0.112	0.102

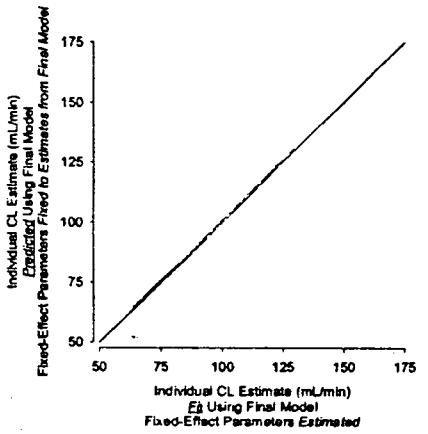
Abbreviations: MPE = mean prediction error; MSPE = mean squared prediction error; MRE = mean relative error.

Further comparison of CL based on fixed parameter using validation set with estimated parameters from the validation set show validity of the model.



POPK.9.10. Frequency distribution of individual estimates of LY231514 clearance

Heavy solid curve: Log-normal distribution of individual CL estimates from the index dataset.
Solid curve: Log-normal distribution of individual CL estimates from the validation dataset (predictions)
Dashed curve: Log-normal distribution of individual CL estimates from the validation dataset (model fit).



Comparison of clearance estimates for the validation dataset

CL 91.6 ml/min
V1 12.9 L
Q 14.4 ml/min
V2 3.38 L
T1/1 3.5 hrs

Protein binding was 81 %, therefore, Fu x GFR = 0.19 x 120 = 23 ml/min for maximal renal clearance. As total clearance I s92 ml/min, active tubular secretion may play an important role in MTA excretion.

Folate deficiency reduced CL. This was not retained in the model.

V1 related to BSA.

Predicted effects of PK

Table POPK.11.1. Effect of Cockcroft-Gault Creatinine Clearance (CGCL) on LY231514 Pharmacokinetic Parameters Following an 870 mg (500 mg/m² • 1.74 m²) Dose Administered as a 10-minute Infusion

CGCL (mL/min)	CL [a] (mL/min)	Peak Concentration [b] (µg/mL)	$AUC_{0-\infty}$ [c] (µg•hr/mL)	$t_{1/2}$ [d] (hr)
36.1 [e]	61.3	66.5	236	4.18
53.9 [f]	70.5	66.2	206	3.88
92.6	90.3	65.7	161	3.50
180 [f]	135	64.5	107	3.13
254 [e]	173	63.6	83.7	3.01

[a] CL = 43.0 + 47.2•CGCL/92.6 where 92.6 is the median baseline CGCL in the analysis population.

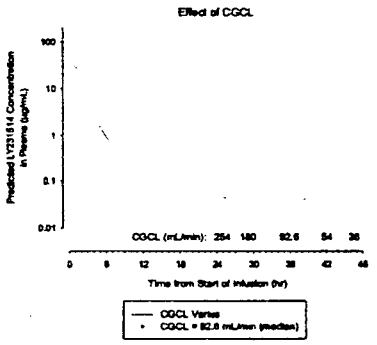
[b] Peak Concentration = predicted concentration (from NONMEM) at 10 minutes from the start of infusion.

[c] $AUC_{0-\infty}$ = Dose/CL

[d] $t_{1/2}$ = terminal elimination half-life calculated based on CL, V_1, Q, and V_2.

[e] Minimum and maximum values in the study population.

[f] 95% tolerance interval of the study population.



Effect of Cockcroft-Gault Creatinine Clearance (CGCL) on Predicted LY231514 Concentrations Following an 870 mg (500 mg/m² • 1.74 m²) Dose Administered as a 10-minute Infusion

Therefore, an individual with CGCL of 30-40 ml/min will have 50% higher AUC than someone with normal CGCL (90 ml/min)

Effect of BSA on V

Table POPK.11.2. Effect of Body Surface Area (BSA) on LY231514 Pharmacokinetic Parameters Following LY231514 Administered as a 10-minute Infusion

BSA (m^2)	Dose (mg)	V_1 [a] (L)	Peak Concentration [b] (µg/mL)	$AUC_{0-\infty}$ [c] (µg•hr/mL)	$t_{1/2}$ [d] (hr)
870 mg Fixed Dose:					
1.21 [e]	870				
1.74	870	12.7	65.7	161	3.50
2.50 [f]	870				
500 mg/m^2 Dose:					
1.21 [e]	600				
1.74	870	12.7	65.7	161	3.50
2.50 [f]	1250				

[a] $V_1 = 6.13 \bullet BSA^{1.32}$

[b] Peak Concentration = predicted concentration (from NONMEM) at 10 minutes from the start of infusion.

[c] $AUC_{0-\infty}$ = Dose/CL where CL is 90.2 (the value for the 'typical' patient in the analysis population, ie. with CGCL of 92.6).

[d] $t_{1/2}$ = terminal elimination half-life calculated based on CL, V_1, Q, and V_2.

[e] Population minimum.

[f] Population maximum.

Cmax affected by BSA. Adjusting dose based on BSA reduces effect on Cmax, but has a large effect on AUC.

Dosing Strategies

The efect of fixed dosing, BSA-based dosing and CGCL based dosing on AUC were evaluated. CGCL was best.

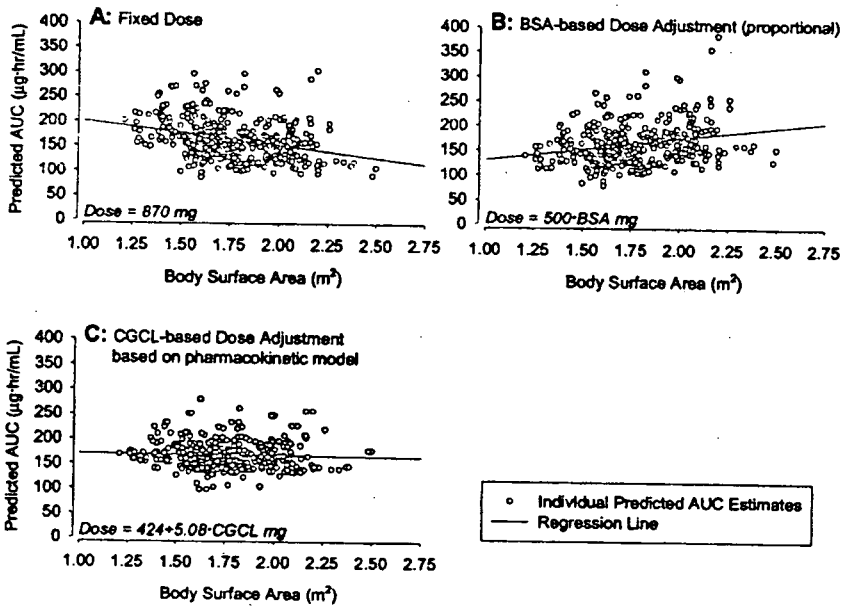


Figure POPK.11.3. Estimated AUC versus BSA by Dosing Strategy

Effect of BSA on V: dosing strategies to minimize effect on Cmax

Fixed dose, BSA-proportional dosing, expontential dosing based on model.

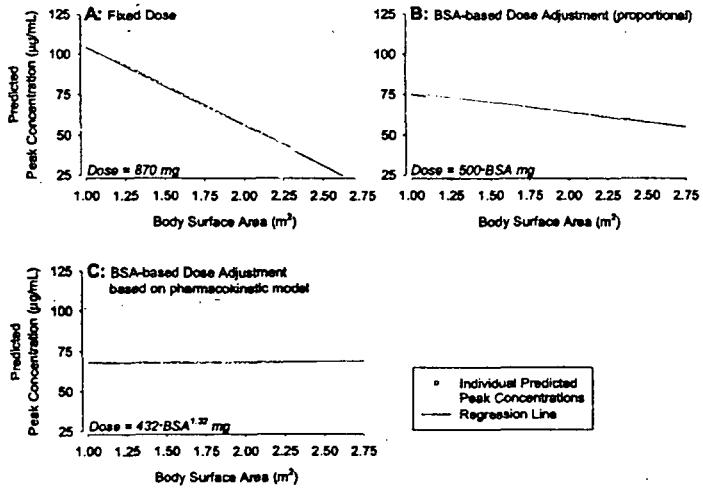


Figure POPK.11.4. Estimated Peak Concentration versus BSA by Dosing Strategy

Conclusions

- 2-C model worked well
- CL decreases as CGCL decreases
- Folate deficiency may decrease CL. Small sample.
- V depends on BSA
- No effect: gender, smoking, age, ethnicity, alcohol, dose, or duration.
- IIV 19.3% for CL 16.6% V124.5% for V2 and 28.4% for residual variability.

JMBQ

Phase III: MTV vs Vinorelbine NSCLC

Terminated due to slow enrollment

Only three patients; no pk analysis, concentrations only
500 mg/m2 once every 3 weeks; 10-min infusion
vinorelbine: 30 mg/m2 weekly iv., every 3 weeks
Analytical

1. JMBZ

Phase II: MTA plus cisplatin NSCLC

MTA 500 mg/m2 10 min i.v. infusion, then 75 mg/m2 cisplatin over 60 minutes Q once every three weeks
432 patients total, 4 for pk. Dense profiles (12 samples over 72 hrs). Noncompartmental pk. ng/ml.

Table JMBZ.1. Patient Characteristics

Patient No.	Gender	Height (cm)	Weight (kg)	BMI (kg/m^2)	BSA (m^2)
10	Male	178	70	22.1	1.87
12	Female	163	71	26.7	1.77
15	Male	170	81	28.0	1.93
16	Female	165	51	18.7	1.55

Table JMBZ.2. Plasma LY231514 Concentrations by Patient

Patient 10		Patient 12		Patient 15		Patient 16	
Time (hr)	Conc. (µg/mL)	Time (hr)	Conc. (µg/mL)	Time (hr)	Conc. (µg/mL)	Time (hr)	Conc. (µg/mL)
0.00	BQL[a]	0.00	BQL	0.00	BQL	0.00	BQL
0.150							
0.250							
0.500							
1.00							
2.00							
4.00							
6.00							
8.00							
23.3							
47.2	BQL				BQL		BQL
71.2	BQL		BQL		BQL		BQL

[a] Below quantitation limit

Table JMBZ.4. LY231514 Pharmacokinetic Parameters

Patient No.	Dose (mg)	Dose (mg/m²)	BSA (m²)	C_{max} (µg/mL)	T_{max} (hr)	$t_{½}$ (hr)	λ_z (1/hr)	Time Interval for $t_{½}$ estimate (hr)
10	915	489						6 – 23.3
12	875	495						5.92 – 47.7
15	960	499						6 – 24
16	770	497						5.92 – 23.6
N	4	4	4	4	4	4	4	
Mean	880	495	1.78	110	0.146	2.91	0.255	
SD	81.1	4.26	0.167	25.3	0.00834	0.987	0.0679	
Min								
Median	895	496	1.82	113.9305	0.1500	2.54	0.273	
Max								
CV (%)	9.22	0.900	9.38	23.0	5.72	33.9	26.6	

Patient No.	Cl_p (mL/min)	CL_p (mL/min/m²)	V_z (L)	V_z (L/m²)	V_{ss} (L)	V_{ss} (L/m²)	$AUC_{0-\infty}$ (hr•µg/mL)	AUC_{0-t} (hr•µg/mL)
10	82.7	44.2	15.8	8.42	10.4	5.57	184	184
12	69.9	39.6	26.4	15.0	13.9	7.87	209	209
15	104	54.0	23.8	12.4	13.6	7.09	154	154
16	113	73.0	23.8	15.4	14.5	9.36	114	114
N	4	4	4	4	4	4	4	4
Mean	92.4	52.7	22.5	12.8	13.1	7.47	165	165
SD	19.6	14.8	4.63	3.19	1.83	1.58	41.0	41.0
Min								
Median	93.4	49.1	23.8	13.7	13.8	7.48	169	169
Max								
CV (%)	21.3	28.1	20.6	25.0	14.0	21.2	24.8	24.9

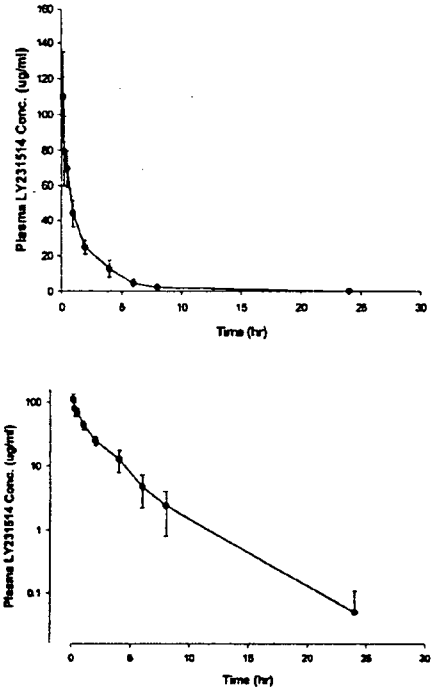


Figure JMBZ.2. Plasma LY231514 Concentration-Time Profile (Mean ± SD; N=4 Patients).

CL: 52.7 ± 14.8 ml/min/m2
Vss: 7.47 ± 1.58 L/m2

T1/2: 2.91 ± 0.99 hr.

Formulation: lyophilized powder of 20, 100 and 500 mg
Sponsor's conclusions
PK consist with previous studies
PK support safe use of ALIMTA/cisplatin.

2. JMAU
Phase 1 MTA and carboplatin in malignant pleural mesothelioma
MTA 400, 500 or 600 mg/m2 once every 21 days as 10-imn infusion. Thirty minutes post MTA, 504 to 1074 mg/m2 of carboplatin were infused over a 30 minutes once every three weeks.
Purpose: determine if MTA affected carboplatin PK. Compared to historical data.
Dense sampling over 24 hrs/ 24-hr carboplatin used to calculate free platin.
Noncompartmental; PK.

Table JMAU.2. Summary of Patient Demographics

Gender	Statistic	Age (yr)	Body Weight (kg)	Body Surface Area (m^2)[1]
Male	mean	58.0	76.8	1.92
(n = 16)	SD	7.9	10.0	0.13
	min	39.4	63	1.75
	max	69.5	103	2.23
Female	mean	60.3	62.5	1.66
(n = 4)	SD	2.1	2.4	0.03
	min	58.4	60.0	1.63
	max	62.5	65.0	1.69

[1] Body surface area obtained from case report form

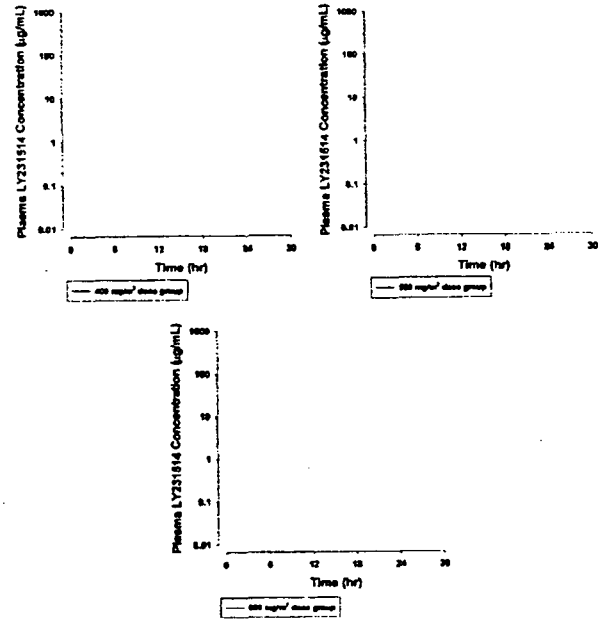
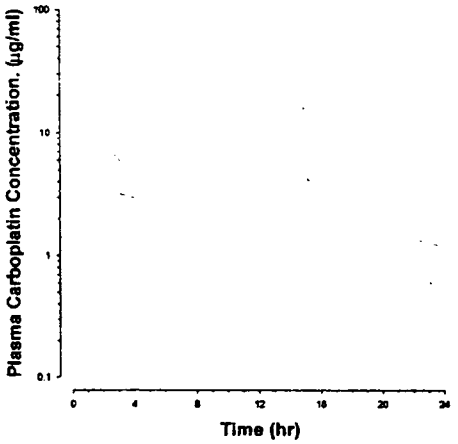


Figure JMAU.2. Individual plasma LY23514 concentration-time profiles by dose group.



Plasma concentrations normalized to the median dose of 765 mg.

Figure JMAU.4. **Individual normalized plasma total platinum concentration-time profiles.**

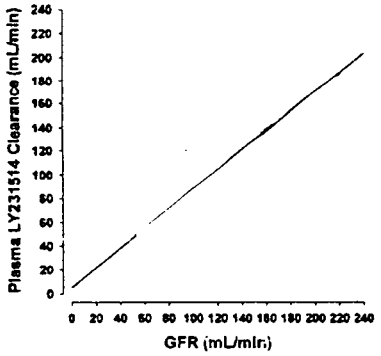


Figure JMAU 6. Relationship between LY231514 clearance and renal function as assessed by measured glomerular filtration rate.

Table JMAU.5. Mean Total Platinum Pharmacokinetic Parameters

Parameter	Arithmetic Mean (CV as %) (n = 20)
C_{max}[b]	23.0
(µg/mL)	(17)
$AUC_{0-\infty}$[b]	93.9
(µg•hr/mL)	(15)
T_{max}	0.57
(hr)[a]	(0.50 – 0.75)
CL_p	136
(mL/min)	(20)
CL_p	72.7
(mL/min/m²)	(16)
V_{ss}	129
(L)	(39)
V_{ss}	68.5
(L/m²)	(37)
$t_{1/2}$	15.6
(hr)	(33)

[a] reported as median (range)

[b] normalized to a carboplatin dose of 400 mg/m²

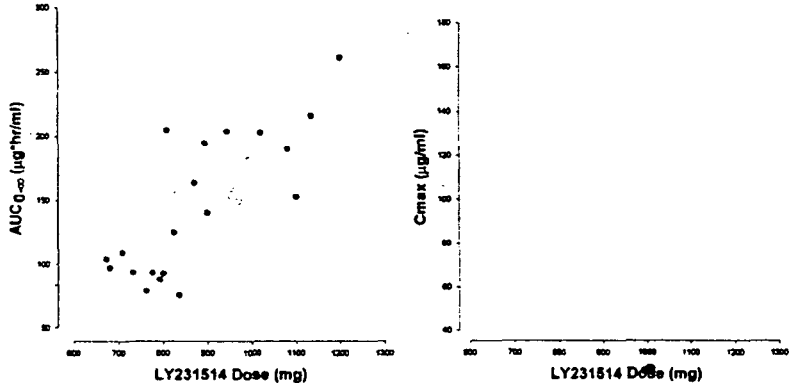


Figure JMAU.5. **Area under the plasma concentration-time curve (left) and maximum plasma concentration (right) as a function of dose.**

Table JMAU.3. **Mean LY231514 Pharmacokinetic Parameters**

Parameter	Arithmetic Mean (CV as %) Dose (mg/m²)		
	400 (n = 9)	500 (n = 8)	600 (n = 3)
C_{max} (µg/mL)	69.3 (17%)	116 (11%)	161 (2.3%)
$AUC_{0-\infty}$ (µg•hr/mL)	92.5 (12%)	174 (18%)	223 (16%)
T_{max} (hr)[a]	0.15 (0.15 – 0.67)	0.18 (0.15 – 0.33)	0.16 (0.15 – 0.17)
CL_p (mL/min)	138 (18%)	91.1 (21%)	86.2 (11%)
CL_p (mL/min/m²)	72.8 (12%)	49.5 (20%)	45.0 (14.2%)
V_{ss} (L)	18.4 (16%)	14.1 (17%)	13.4 (5.5%)
V_{ss} (L/m²)	9.75 (11%)	7.64 (15%)	7.01 (7.3%)
$t_{1/2}$[b] (hr)	2.8 (13%)	2.8 (7.7%)	2.9 (7.7%)

[a] median (range)

MTA: AUC and Cmax increased greater than proportionally with dose****differs from MTA alone
Carboplatin: only two data samples. Ghazal-Aswad method to calculate free platinum "was reasonably consistent" generated by actual samples.
Ultrafilterable platinum t1/2 2 (1.8 to 3hrs), 37 hrs for total platinum.

MTA formulation: 100 or 500 mg aqueous solution.
Samples: 14 over 24 hrs for mTA
13 over 24 hrs for carboplatinum

MTA analysis: [redacted] ng/ml
Carboplatinum: atomic absorption of total platinum in plasma 50 to 2221 ng Pt/ml

Comments
Carboplatin elimination t1/2 of 15 hrs based on 2 points. At least 2-c model pk. Free pt not measured; calculated according to Ghazal Aswad 1966
AUC = C24 + 0.33/0.82
Compared to historical data; no direct comparison within patient group.

3. JMAR
Phase 1 MTA and 5-FU in advanced or metastatic cancer.
2 patients; concentrations no analysis

MTA 300, 400 or 500 mg/m2 as a 10-min infusion once every three weeks
5-FU 250, 300, 350, 400, 450 and 500 mg/m2 as a bolus daily for 5 days. 5-FU administered after MTA.
MTA analysis: —— ng/ml
MTA formulation: lyophilized powder, 100mg/vial
MTA sampling: 0, end of infusion, 1,2 , 4, 8 and 24 hrs post-infusion
5-FU sampling: 0, 1, 9, 24, 144, 153 168 hrs pot infusion, then 15, 30 and 60 min post infusion-stop on day 8

Comments

No 5-FU data listed-look further for data and number of patients and 5-FU assay.

4. JMAP
Phase 1 MTA and Cisplatin in locally advanced or metastatic solid tumors
Objective: PK of MTA and total platinum

Dose escalation design
MTA starting at 300 mg/m2 Cisplatin 60 mg/m2 30 minutes after MTA, or MTA day 1 (treatment A) and cisplatin day 2 (treatment B)
MTA formulation: lyophilized white powder 100 mg/vial
MTA analysis —— ng/ml.
Total platinum from Cisplatin atomic absorption from 95 to 3250 ng Pt/ml- ——

Table JMAP.1 Summary of Patient Demographics

Gender	Statistic	Age (yr)	Body Weight (kg)	Body Surface Area (m^2)[1]
Male	mean	59.0	70.0	1.84
	CV%	18	22	12
	min	37.0	44.6	1.45
	max	72.0	93.5	2.16
Female	mean	50.0	63.7	1.65
	CV%	31	36	19
	min	28.0	36.0	1.20
	max	66.0	100.0	2.09

[1] Body surface area obtained from case report form

MTA plasma sampling: 14 samples over 24 hrs for treatment A, 27 samples over 96 hrs treatment B Urine: 24 and 48 cumulative.
Total PT: 10 samples over 23 hrs

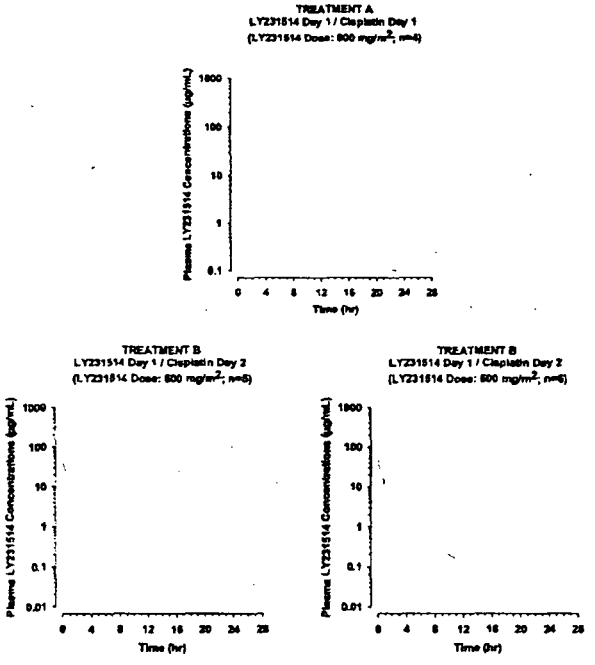


Figure JMAP.1 Individual plasma LY231514 concentration-time profiles by dose group and treatment.

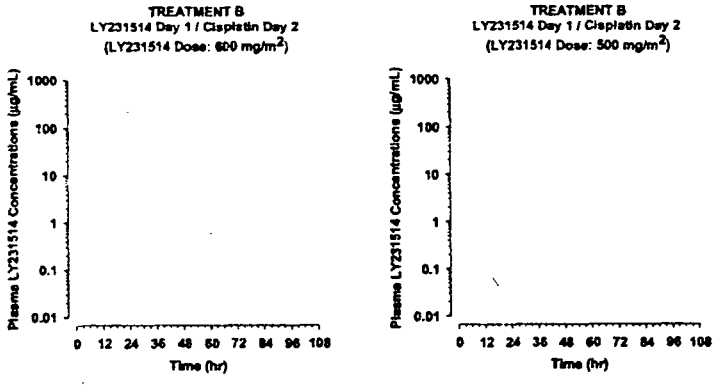


Figure JMAP.2 Individual plasma LY231514 concentration-time profiles by dose group and treatment over the entire blood sampling period.

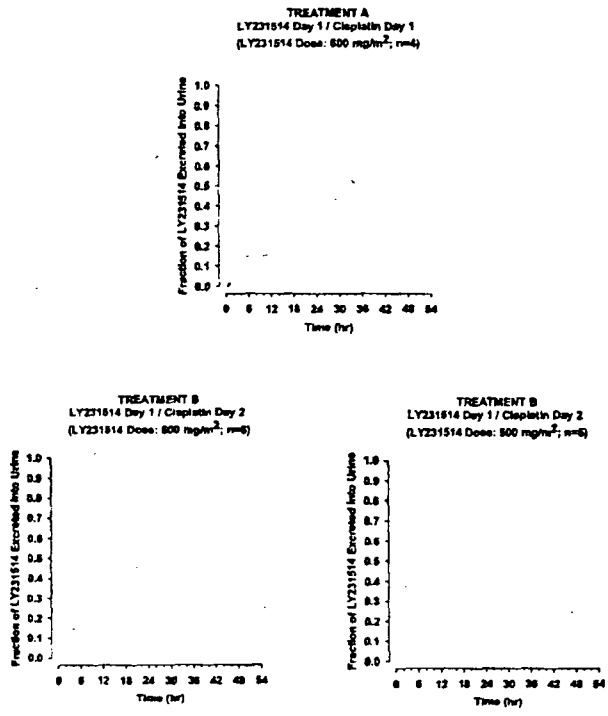


Figure JMAP.3 Individual plots of cumulative fraction of LY231514 excreted unchanged in urine over 48 hours by dose group and treatment.

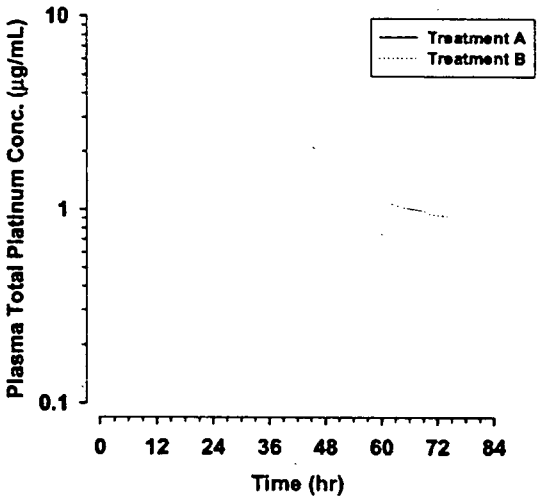


Figure JMAP.4 **Individual plasma total platinum concentration-time profiles.**

Table JMAP.2 **Mean LY231514 Pharmacokinetic Parameters**

Parameter	Arithmetic Mean (CV as %) Dose (mg/m²) 600 (Treatment A) n=4	500 (Treatment B) n=6	600 (Treatment B) n=5
C_{max} (µg/mL)	83.1 (21%)	72.2 (49%)	97.1 (21%)
$AUC_{0-\infty}$ (µg•hr/mL)	158 (25%)	120 (47%)	146 (44%)
T_{max} (hr)[a]	0.2 (0.2 – 0.4)	0.2 (0.2 – 0.4)	0.2 (0.2 – 0.2)
CL_p (mL/min)	107 (41%)	162 (58%)	141 (31%)
CL_p (mL/min/m²)	67.2 (30%)	90.1 (63%)	77.0 (33%)
V_{ss} (L)	20.8 (42%)[c]	23.9 (45%)[c]	21.3 (28%)[c]
V_{ss} (L/m²)	12.9 (31%)[c]	13.2 (50%)[c]	11.4 (22%)[c]
Fe	0.32 (79%)	0.38 (32%)	0.48 (48%)
CL_r (mL/min)	42.7 (112%)	56.9 (56%)	66.6 (44%)
CL_r (mL/min/m²)	25.1 (106%)	31.6 (61%)	38.3 (58%)
$t_{1/2}$[b] (hr)	3.4	2.8	3.1
		30.4[c]	37.6[c]

[a] median (range)
[b] harmonic mean
[c] half-life of long terminal phase

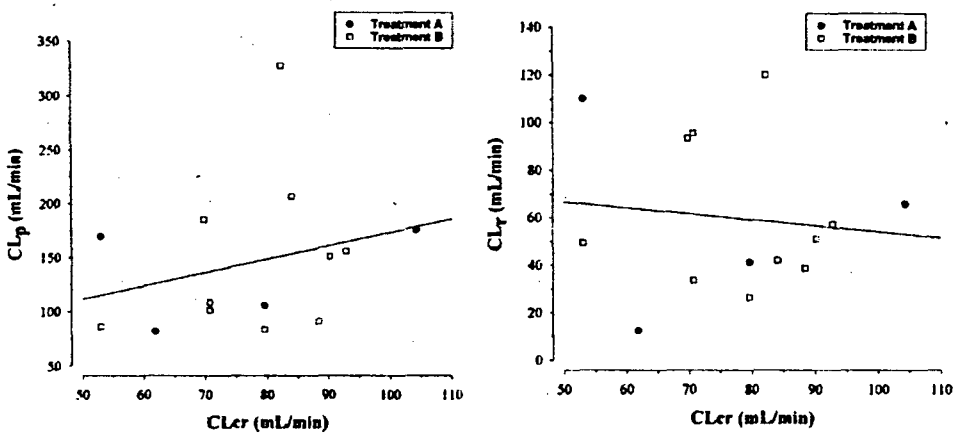


Figure JMAP.5 **Relationship between total plasma clearance, renal clearance, and calculated creatinine clearance.**

Table JMAP.3 **Mean Total Platinum Pharmacokinetic Parameters**

	Arithmetic Mean (CV as %) Dose (mg/m²)	
Parameter	75 (Treatment A) n=4	75 (Treatment B) n=7
C_{max}	2.58	2.62
(µg/mL)	(17%)	(11%)
$AUC_{0-\infty}$	180.0	184.8
(µg•hr/mL)	(57%)	(20%)
T_{max}	2.0	2.0
(hr)[a]	(no range)	(1.8 – 2.2)
CL_p	14.8	12.9
(mL/min)	(75%)	(37%)
CL_p	9.31	7.12
(mL/min/m²)	(65%)	(29%)
V_{ss}	61.1	80.0
(L)	(24%)	(14%)
V_{ss}	38.7	44.8
(L/m²)	(13%)	(14%)
$t_{1/2}$[b]	50.4	67.1
(hr)		

[a] median (range)
[b] harmonic mean

Table JMAP.3.1. Geometric Means and P-values of LY231514 Pharmacokinetic Parameters for Treatments A and B (Log-Transformed Data)

Parameter [a]	Geometric Mean Treatment A	Geometric Mean Treatment B	Ratio or Difference of Means [b]	Significance p-Value
LY231514				
C_{max}	75.02	88.04	0.85	0.53
$AUC_{0-\infty}$	149.0	134.0	1.11	0.72
CLp	66.9	74.9	0.89	0.71
CLr	14.89	30.81	0.48	0.17
Fe	0.28	0.44	-0.16	0.25
Vss	13.68	12.13	1.55	0.64

[a] Units for parameters: C_{max} (µg/mL), $AUC_{0-\infty}$ (µg•hr/mL), CL_p (mL/min/m²), CL_r (mL/min/m²), and V_{ss} (L/hr/m²).

[b] Analyses of C_{max}, $AUC_{0-\infty}$, CL_p, and CL_r parameters are based on log-transformed data. Antilogs of transformed scale Treatment A minus Treatment B differences supply a ratio estimate. Analyses of Fe and Vss parameters are based on untransformed data.

Table JMAP.5.1. Geometric Means and P-values of Total Platinum Pharmacokinetic Parameters for Treatments A and B (Log-Transformed Data)

Parameter [a]	Geometric Mean Treatment A	Geometric Mean Treatment B	Ratio or Difference of Means [b]	Significance p-Value
Total Platinum				
C_{max}	2.55	2.60	0.98	0.83
$AUC_{0-\infty}$	156.6	180.5	0.87	0.62
CLp	7.98	6.92	1.15	0.62
λ_z	0.0137	0.0104	0.0033	0.44
Vss	38.84	44.69	-5.84	0.16

[a] Units for parameters: C_{max} (µg/mL), $AUC_{0-\infty}$ (µg•hr/mL) and CL_p (mL/min/m2), V_{ss} (L/hr/m2), and λ_z. (hr^{-1})

[b] Analyses of C_{max}, $AUC_{0-\infty}$ and CL_p parameters are based on log-transformed data. Antilogs of transformed scale Treatment A minus Treatment B differences supply a ratio estimate. Analyses of λ_z and V_{ss} parameters are based on untransformed data.

PT: long terminal elimination: Check historical t1/2
T1/2: intermediate (from 24 hr data) was 3 hrs; from prolonged measurement: 30 hrs
No apparent relationship between CL, CLr and CLcr; due to mostly normal renal function (sponsor)
Conclusions(sponsor)
Cisplatin did not affect mTA PK
MTA did not affect Cisplatin PK

NOTES: no patient appeared to receive less than 500 mg/m2 of ALIMTA; renal function ranged from 53 to 140 ml/min; cisplatin infusions were 2 hrs and dosed at 75 mg/m2 approximately

5. JMAB-Addendum
Phase 1 MTA as a bolus once every 7 days
Data originally analyzed assuming bolus administration (MIKAPC). Re-analyzed noncompartmentally using infusion (10 min) WinNonLin.
Some differences in the kinetics; re-plotted some figures

APPEARS THIS WAY
ON ORIGINAL

Table JMAB.1. Comparison of Mean LY231514 Pharmacokinetic Parameters by Dose Group

	10 mg/m^2 (n=4)		20 mg/m^2 (n=4)		30 mg/m^2 (n=10)		40 mg/m^2 (n=7)	
Parameter	MIKAPC	WinNonlin	MIKAPC	WinNonlin	MIKAPC	WinNonlin	MIKAPC	WinNonlin
C_{max} (µg/mL)[a]	2.01 (20%)	2.01 (20%)	4.32 (14%)	4.32 (14%)	7.48 (17%)	7.48 (17%)	11.2 (40%)	11.2 (40%)
$AUC_{0-\infty}$ (µg•hr/mL)[a]	2.57 (50%)	2.27 (55%)	5.91 (27%)	5.49 (27%)	13.6 (35%)	12.0 (24%)	14.4 (42%)	12.9 (42%)
T_{max} (hr)	0.083 – 0.25[c]	0.083 0.083 – 0.25[b]	0.083 – 0.25[c]	0.083 0.083 – 0.25[b]	0.083 – 0.25[c]	0.25 0.083 – 0.25[b]	0.083 – 0.25[c]	0.25 0.083 – 0.25[b]
CL_p (mL/min)[a]	NR	155 (47%)	NR	113 (40%)	NR	80.6 (29%)	NR	112 (37%)
CL_p (mL/min/m^2)[a]	79.2 (49%)	93.4 (47%)	59.6 (27%)	64.4 (27%)	39.6 (24%)	46.4 (29%)	52.3 (34%)	58.3 (34%)
V_{ss} (L)[a]	NR	14.5 (20%)	NR	11.3 (27%)	NR	12.4 (21%)	NR	16.3 (29%)
V_{ss} (L/m^2)[a]	6.31 (16%)	8.56 (22%)	5.70 (8.6%)	6.47 (8.6%)	5.63 (23%)	7.13 (14%)	6.64 (16%)	8.53 (26%)
$t_{1/2}$ (hr)	1.3[d]	1.4 (36%)[a]	1.5[d]	1.5 (5.6%)[a]	2.1[d]	2.3 (30%)[a]	2.0[d]	2.2 (39%)[a]

[a] reported as arithmetic mean (%CV)

[b] reported as median (range)

[c] report as range

[d] reported as harmonic mean only

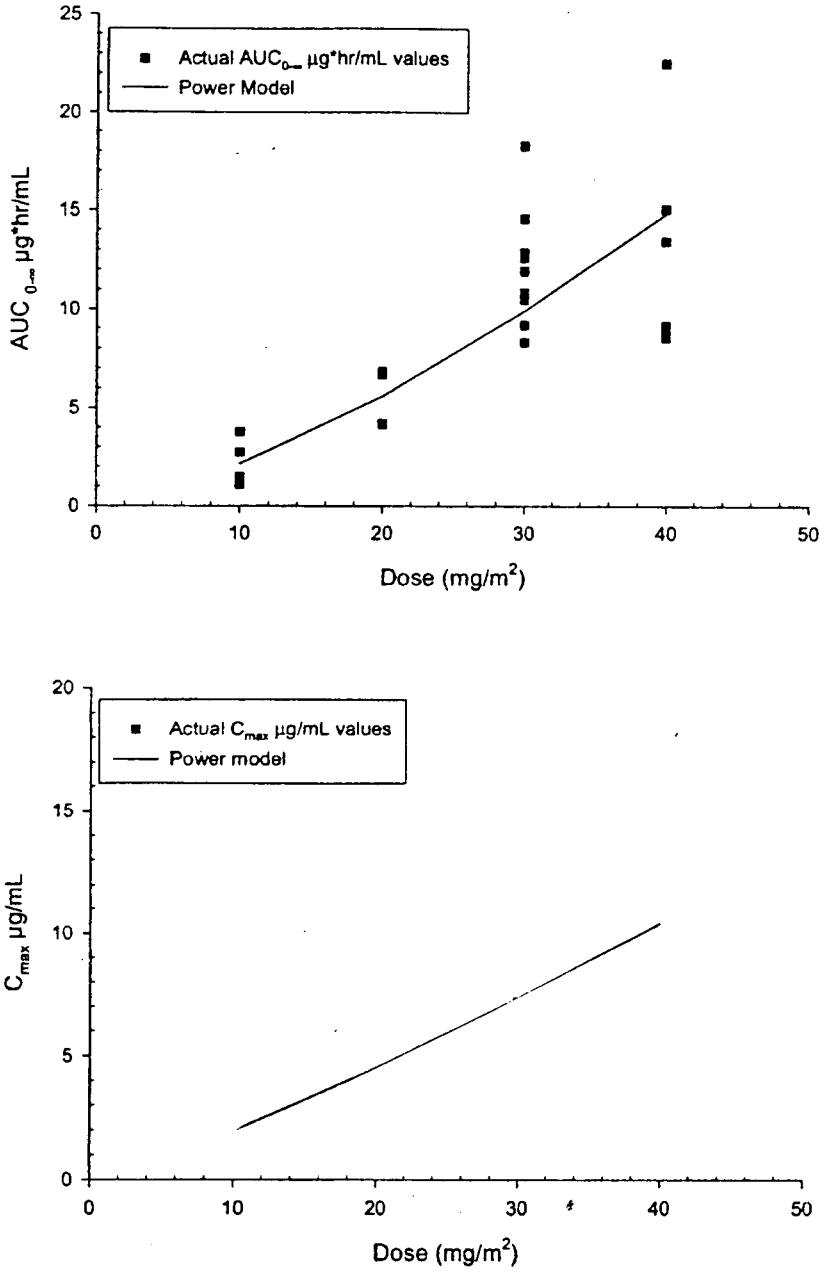


Figure JMAB.6. **Results from assessment of dose proportionality for $AUC_{0-\infty}$ and C_{max} for BSA normalized dose (mg/m^2).**

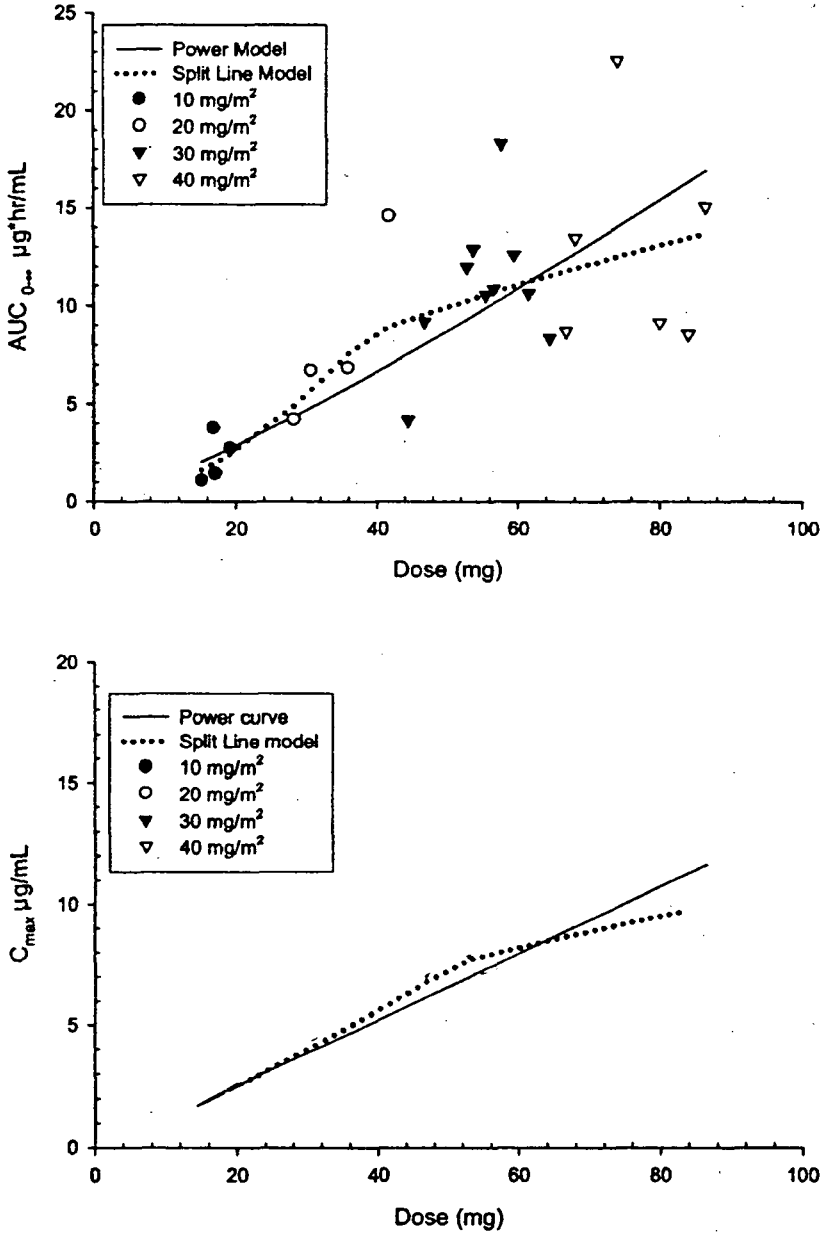


Figure JMAB.7. **Results from assessment of dose proportionality for $AUC_{0-\infty}$ and C_{max} for total dose (mg).**

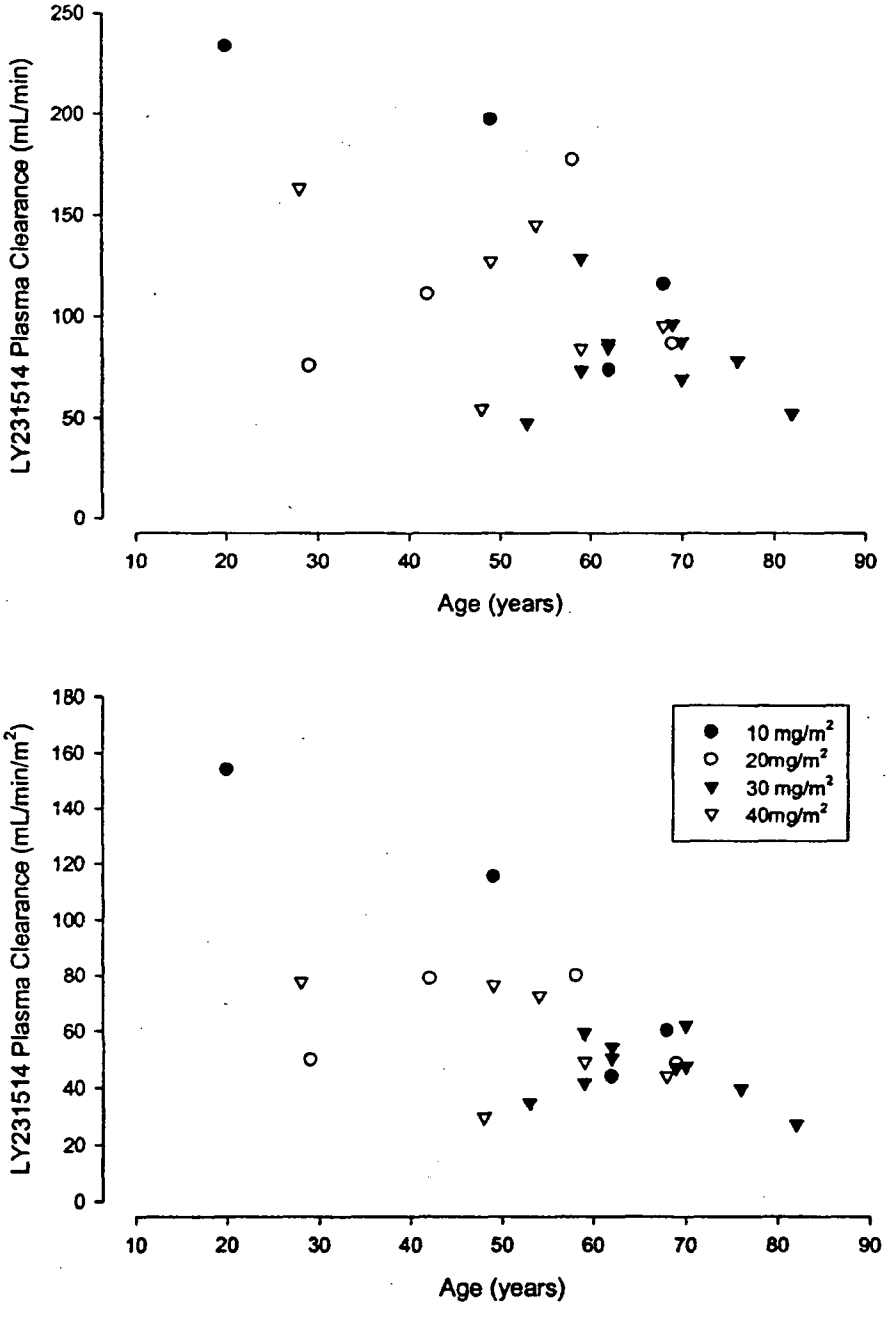


Figure JMAB.5. **Relationship between CL_p (mL/min and mL/min/m^2) and age.**

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

Parameter	Power model	
	Slope (90% CI)	DP ratio
$AUC_{0-\infty}$ µg*hr/mL (BSA normalized dose)	1.40 (1.12, 1.68)	1.39
C_{max} µg/mL (BSA normalized dose)	1.21 (1.03, 1.39)	1.78
$AUC_{0-\infty}$ µg*hr/mL (total dose)	1.21 (0.94, 1.49)	1.58
C_{max} µg/mL (total dose)	1.04 (0.85, 1.24)	2.57

Note: DP – dose proportional

Table JMAB.3. **Results from Dose Proportional Assessments for $AUC_{0-\infty}$ with age as covariate**

Parameter	Power model with age	
	Slope (90% CI)	DP ratio
$AUC_{0-\infty}$ µg*hr/mL (BSA normalized)	1.31 (1.08, 1.53)	1.52
$AUC_{0-\infty}$ µg*hr/mL (total dose)	1.12 (0.85, 1.38)	1.79

Notes: DP – dose proportional ratio

Sponsor's conclusions
MTA: small Vss, moderate Cl, short t1/2 (1-3 hrs)
Cl related to renal function
CL related to age. As age increases, Cl decrease in CL
AUC and Cmax increased more than proportionally to dose; small and not clinically significant

6. 7. JMAA-Addendum
Phase 1 MTA as a bolus once every 21 days
Data originally analyzed assuming bolus administration (MIKAPC). Re-analyzed noncompartmentally using infusion (10 min) WinNonLin.

Sponsor's conclusions
MTA small V, moderate CL, short t1/2
Cl dependent upon renal function

Table JMAA.1. Comparison of Mean LY231514 Pharmacokinetic Parameters by Dose Group During Cycle 1

	525 mg/m² (n=4)		600 mg/m² (n=20)		700 mg/m² (n=4)	
Parameter	MIKAPC	WinNonlin	MIKAPC	WinNonlin	MIKAPC	WinNonlin
C_{max}[a] (ng/mL)	121 (13%)[b]	118 (15%)	137 (33%)	137 (33%)	175 (27%)[f]	166 (29%)
$AUC_{0-\infty}$[a] (ng•hr/mL)	231 (32%)[b]	193 (36%)	266 (27%)	239 (26%)	398 (43%)[f]	347 (41%)
T_{max} (hr)	0.08 – 0.25[c]	0.25[d] 0.08 – 0.25[e]	0.08 – 0.25[c]	0.25[d] 0.08 – 0.5[e]	0.08 – 0.25[c]	0.25[d] 0.08 – 0.25[e]
CL_p[a] (mL/min)	NR	94.8 (28%)	NR	85.1 (23%)	NR	71.4 (37%)
CL_p[a] (mL/min/m²)	40.7 (33%)[b]	49.3 (31%)	40.0 (24%)	45 (24%)	33.6 (39%)[f]	45.9 (34%)
V_{ss}[a] (L)	NR	14.3 (19%)	NR	15.6 (26%)	NR	14.0 (12%)
V_{ss}[a] (L/m²)	6.85 (25%)[b]	7.2 (11%)	7.00 (20%)	8.08 (19%)	6.39 (2.7%)[f]	7.44 (18%)
$t_{1/2}$ (hr)	3.94[c]	4.1[e] (36%)	3.1[f]	4.3[e] (31%)	3.7[f]	4.9[e] (30%)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from the start of infusion through infinity; CL_p = plasma clearance; C_{max} = maximum p concentration; CV = coefficient of variation = [standard deviation/mean] x 100%; hr = hour; NR = Not Reach; $t_{1/2}$ = apparent terminal elimination half-

T_{max} = observed sampling time of C_{max}; V_{ss} = distribution volume at steady state.

a reported as arithmetic mean (%CV).
b reported as median (range).
c reported as harmonic mean only.
d reported as harmonic mean only.
e n = 3.
f n = 5.

Figure JMAA.1. **Relationship between CL_p with dose and body surface area normalized dose.**

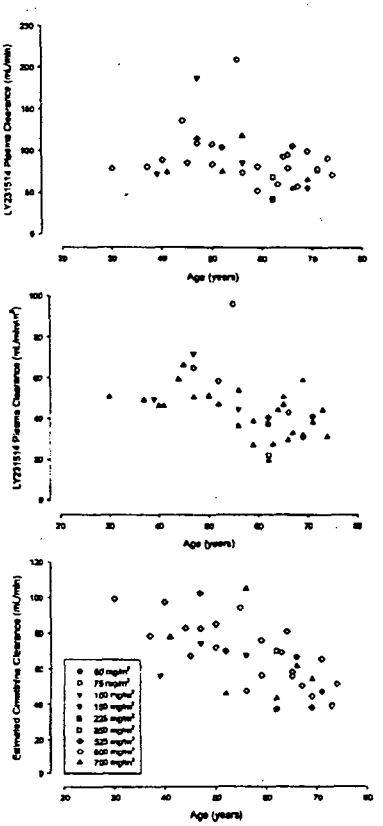


Figure JMAA2. Relationship between LY231514 plasma clearance (CLp, mL/min and mL/min/m^2) and lean body mass estimated creatinine clearance (mL/min) with age.

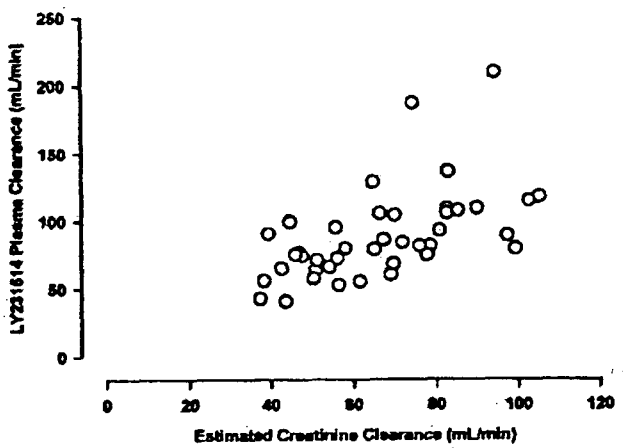


Figure JMAA3. Relationship between LY231514 plasma clearance with lean body mass estimated creatinine clearance.