AAC Accepts, published online ahead of print on 15 June 2009
Antimicrob. Agents Chemother. doi:10.1128/AAC.00106-09

Safety, Tolerability, and Pharmacokinetics of PA-824 in Healthy Subjects

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Keywords: PA-824, safety, tolerability, pharmacokinetics, tuberculosis, nitroimidazole, nitroimidazo-oxazine

Running Title: Safety, Tolerability, and Pharmacokinetics of PA-824

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ABSTRACT

PA-824 is a novel antibacterial agent that has shown in vitro activity against both drug-sensitive and drug-resistant *Mycobacterium tuberculosis*. The compound's MIC is between 0.015 and 0.25 µg/mL for drug-sensitive strains and between 0.03 and 0.53 µg/mL for drug-resistant strains. In addition, it is active against nonreplicating anaerobic *Mycobacterium tuberculosis*. The safety, tolerability, and pharmacokinetics of PA-824 were evaluated in two escalating-dose clinical studies, one a single-dose study and the other a multiple-dose study (up to 7 days of daily dosing). In 58 healthy subjects dosed with PA-824 across these studies, the drug candidate was well tolerated with no significant or serious adverse events. In both studies, following oral administration, PA-824 reached maximal plasma levels in 4 to 5 hours, independent of dose. Maximal blood levels averaged approximately 3 µg/mL (1500 mg dose) in the single-dose study and 3.8 µg/mL (600 mg dose) in the multiple-dose study. Steady state was achieved after 5 to 6 days of daily dosing, with an accumulation ratio of approximately 2. The elimination half-life averaged 16 to 20 hours. Overall, PA-824 was well tolerated following oral doses once daily for up to 7 days, and pharmacokinetic parameters were consistent with a once-a-day regimen. The results of these studies, combined with the demonstrated activity of PA-824 against drug-sensitive and multidrug-resistant *Mycobacterium tuberculosis*, support investigation of this novel compound for the treatment of tuberculosis.

INTRODUCTION

According to the World Health Organization, there were 9.27 million new tuberculosis (TB) cases worldwide in 2007, which claimed the lives of approximately 1.77 million people, including 456,000 patients co-infected with HIV (10). In addition, global increases in cases of multidrug-resistant TB and, more recently, extensively drug-resistant TB pose serious treatment challenges (11). New anti-TB drugs are needed that can shorten the duration of treatment, improve the treatment of resistant disease, facilitate treatment of TB patients coinfected with HIV, and shorten treatment of latent TB infection.

The 4-nitroimidazo-oxazoles (a subclass of nitroimidazoles) have potent sterilizing activity against *Mycobacterium tuberculosis* (*M. tb.*), as first demonstrated in 1993 (1). Further investigation of nitroimidazoles in an anaerobic model of *M. tb.* dormancy demonstrated that metronidazole is active against slow-growing *M. tb.*, suggesting the potential for treatment of latent TB infection and for shortening treatment of active TB disease (9). Further development of the nitroimidazole class by Pathogenesis, Inc., led to the discovery of another subclass, 4-nitroimidazo-oxazines, with promising activity against *M. tb.* PA-824—full chemical name (S)-2-nitro-6-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine)—was identified as the lead 4-nitroimidazo-oxazine. Stover et al. (7) reported that the MIC of PA-824 under aerobic conditions against a variety of drug-sensitive clinical isolates was similar to the MIC of isoniazid (MIC of PA-824, 0.015 to 0.25 µg/mL; MIC of isoniazid, 0.03 to 0.06 µg/mL). PA-824 was also found to be active against all single-drug and multidrug-resistant clinical isolates of *M. tb.* tested, with MICs of 0.03 to 0.53 µg/mL.

Additional studies using microaerophilic and anaerobic culture models indicated that PA-824 is also active against both replicating and nonreplicating or infrequently replicating *M. tb.* (2, 7).

Like metronidazole, PA-824 requires metabolic activation by *M. tb.* through an F420-dependent nitro-reduction (3, 4, 7). Although not thoroughly elucidated at this time, PA-824's novel mechanism of action involves inhibition of the synthesis of both protein and lipids, but not nucleic acid. Studies by Stover et al. (7) demonstrated that PA-824 inhibits the oxidation of hydroxymycolate to ketomycolate, an essential lipid for *M. tb.* cell wall function. Recent work by Singh et al. (6) indicates that reduction of PA-824 to its des-nitroimidazole metabolite by a deazaflavin (F420)-dependent nitroreductase is associated with generation of reactive nitrogen species, including nitric oxide, which may represent important effectors of PA-824 killing of *M. tb.* under anaerobic conditions. In an experimental mouse model of infection, Tyagi et al. (8) demonstrated that, at a dose of 100 mg/kg, PA-824 has substantial bactericidal activity during both the initial and continuation phases of TB treatment. Using a short-course mouse infection model that employs 9 days' drug treatment of γ-interferon knockout mice infected with *M. tb.* 14 days before treatment initiation, Lenaerts et al. (2) found that at 100 mg/kg PA-824 was as active as isoniazid at 25 mg/kg, rifampin at 10 mg/kg, and moxifloxacin at 100 mg/kg. Additional studies in a mouse model of TB examined the activity of PA-824 administered in combination with current TB drugs. When substituted for isoniazid in standard therapy, PA-824 resulted in significantly fewer colony-forming units after 2 months of therapy and a faster rate of conversion to culture negativity than the standard drug combination. Relapse rates after 6 months of treatment were not different in the

experimental and control treatment arms in this study, but the study design was such that an improved relapse rate relative to control could not have been demonstrated (5). Pharmacokinetic analyses reported by Nuermberger et al. (5) demonstrated in mice that the standard rifampin-isoniazid-pyrazinamide regimen does not affect core PA-824 pharmacokinetic parameters, such as C_{max} (maximum concentration observed), AUC_{0-24} (total area under concentration-time curve, 24 hours), or $t_{1/2}$ (half-life). Further nonclinical studies are underway to characterize PA-824's activity and interactions in novel drug combinations.

MATERIALS AND METHODS

This report examines the data from two Phase I clinical studies designed to assess the safety, tolerability, and pharmacokinetics of PA-824: an ascending, single-dose study (CL-001) and an ascending multiple-dose study (CL-002). The studies were conducted at MDS Pharma Services facilities in Lincoln, Nebraska (CL-001), and Neptune, New Jersey (CL-002). For each study, the ascending doses were administered to separate groups of PA-824-naïve subjects enrolled serially during the study.

Study design. Study CL-001 was a double-blind, placebo-controlled, single-dose, dose-escalating, pharmacokinetic, tolerability, and safety study in healthy adult male volunteers. Single oral doses (50, 250, 500, 750, 1000, 1250, or 1500 mg) or placebo in a tablet formulation were administered to seven groups of healthy subjects after an overnight fast. Six groups consisted of eight subjects each, with six subjects in each group receiving PA-824 and two receiving placebo. The 50 mg dose group had five subjects (four received PA-824 and one received placebo).

Study CL-002 was a double-blind, placebo-controlled, multiple-dose, dose-escalating, pharmacokinetic, tolerability, and safety study in healthy adult male and female volunteers. The study design included four dose groups of eight subjects each (six received PA-824 and two received placebo) receiving doses of 200, 600, 1000, and 1400 mg of PA-824 or placebo in tablet form each day for 7 days after an overnight fast. Because of an observed increase in serum creatinine levels in the 1000 mg dose group, dosing of that cohort was halted on Day 5 and the 1400 mg dose cohort was not enrolled. Dose groups were enrolled sequentially for both studies, and safety was assessed prior to enrolling the next group.

Subjects. Healthy male volunteers were recruited for Study CL-001; healthy male and female volunteers were recruited for Study CL-002. Inclusion and exclusion criteria were identical for both studies, with the exception that Study CL-002 specified criteria reflecting the inclusion of women. All subjects were aged 19 to 50, and none had any clinically significant findings in their medical history, clinical laboratory results, 12-lead electrocardiograms, or physical examination. Subjects were excluded if they had taken any systemic or topical prescription medication, with the exception of hormonal contraceptives for women, in the 14 days prior to dosing or during the study. Subjects who had taken over-the-counter medications (including vitamins, herbal preparations, antacids, cough medications, and cold medications) for 7 days prior to dosing or during the study were also excluded, as were subjects who within 30 days of dosing or during the study had taken any drugs of abuse or therapeutic drugs known to (a) be strong inhibitors or inducers of cytochrome P450 enzymes, (b) prolong the QT interval, or (c) alter any major organ function. All study protocols and consent forms were reviewed and

approved by Institutional Review Boards constituted and operating per the U.S. Code of Federal Regulations. All subjects provided written informed consent prior to initiation of the study in which they were participating. Subject safety was assured during the study by means of urinalysis; clinical chemistry, hematology, and coagulation testing; 12-lead electrocardiograms; physical exams and vital signs measurement; and self-reporting of adverse events and regular direct adverse event query.

Sampling. In the single-dose study (CL-001), blood samples (1 x 6 mL) were collected prior to dosing and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 30, and 36 hours post-dose, as well as 7 days post-dose. For the 1250 mg and 1500 mg dose groups, urine was collected at 4-hour intervals starting from the time of dosing through 36 hours post-dose.

In the multiple-dose study (CL-002), blood samples (1 x 6 mL) were collected as follows: pre-dose each day during the treatment period; 1, 2, 3, 4, 5, 6, 7, 8, 12, and 16 hours after dosing on Days 1 and 7; 24, 30, and 36 hours after Day 7 dosing (i.e., during Day 8); daily during washout on Days 9–13, at the time daily dosing would have otherwise occurred; and during Checkout on Day 14. A full urinalysis panel was performed at Screening, Check-in (Day 0), on Day 4, 24 hours after the last dose (Day 8), and at study completion (Day 14), or on early withdrawal from the study. In addition, creatinine clearance and total urinary protein excretion were determined as follows: (a) baseline 12-hour creatinine clearance and total urinary protein excretion starting at Check-in on Day 0 and concluding before dosing on Day 1; and (b) for the 200 mg and 600 mg dose groups, post-dose 24-hour creatinine clearance and total urinary protein excretion measurements started at Hour 0 of Days 2, 5, and 13. In the 1000 mg dose

group, creatinine clearance and urine protein excretion measurements were taken on Days 2, 5, 6, and 11.

Bioanalytical methods. Blood samples were collected and centrifuged, and plasma was separated and stored at −20°C. Urine samples were aliquotted and stored at –20°C. Plasma and urine samples were analyzed for PA-824 using validated liquid chromatography/mass spectrometry methods developed at Covance Laboratories.

PA-824 and the internal standard, triazolam (which was added during sample processing), were extracted from human plasma samples using liquid-liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed using liquid chromatography with tandem mass spectrometric detection. The analytical column used for plasma samples was a Chromolith Speed ROD RP-18e, 50 x 4.6 mm, Merck, Prefilter, Upchurch. Mass spectrometer analysis was conducted with a Sciex API 3000 with ionization using positive ion electrospray. The standard curve range was from 10 to 10,000 ng/mL for PA-824, using a sample volume of 0.0500 mL. The limit of quantitation was 10.0 ng/mL. The accuracy of the curve ranged from 92.2% to 105%, and the relative standard deviation was < 4.8% for the 12 analytical runs employed. Overall recovery efficiency for PA-824 in human plasma was 71.7% for PA-824 and 72.9% for the internal standard.

Pharmacokinetic analysis. Pharmacokinetics were assessed by measuring serial plasma concentrations of PA-824. The pharmacokinetic parameters determined in these two studies include the following: $t_{1/2}$ (elimination half-life), C_{max}, T_{max} (time at which C_{max} occurs), and CL/F (oral clearance) on Days 1 and 7; $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ (area under concentration-time curve extrapolated to infinity) on Day 1; and C_{min} (the steady-

state trough concentration) and $AUC_{(0-\tau)}$ (area under the concentration-time curve during the dosing interval) on Day 7. These parameters were calculated by applying a noncompartmental approach using WinNonlin Professional Version 4.0 (Pharsight Corporation, Mountain View, CA).

AUCs were calculated using linear trapezoidal summation from time zero to the specified timepoint (24 hour, 36 hour, the last available timepoint, or infinity). Elimination half-life ($t_{1/2}$) values were estimated by fitting a line to the last portion of the plasma concentration profile using a least-squares approach.

The parameter values were read into SAS data sets, and all descriptive and plasma inferential statistics were calculated in SAS Version 8.2 (SAS Institute, Inc., Cary, NC). Plasma concentrations and pharmacokinetic parameters of PA-824 were listed and summarized with descriptive statistics (number of subjects [N], mean, median, standard deviation [SD], standard error of the mean [SEM], coefficient of variation [CV%], minimum [min], and maximum [max]). For C_{max}, C_{min}, and $AUC_{(0-24)}$, geometric (geom.) mean and geom. CV% were also calculated. Descriptive statistics for log-transformed pharmacokinetic parameters of $AUC_{(0-24)}$ (Day 1), $AUC_{(0-\tau)}$ (Day 7), C_{min} (Day 7), and C_{max} (Days 1 and 7) for PA-824 were calculated for each group.

RESULTS

A total of 77 healthy male and female subjects participated in the two clinical studies addressing PA-824 safety, tolerability, and pharmacokinetics, with 58 subjects receiving PA-824 and 19 receiving placebo. These 77 participants represented a racially diverse sample population. The multiple-dose study (CL-002) was ended early because of an observed increase in serum creatinine, later determined to be reversible and not caused

by a decrease in glomerular filtration rate (reported in detail in [cross-reference to companion publication in this issue]).

Pharmacokinetics. Plasma concentrations for the single-dose study (CL-001) are shown in Figure 1 and for the multiple-dose study in Figure 2. Key pharmacokinetic parameters across the single-dose and multiple-dose studies are provided in Tables 1 and 2, respectively. PA-824 was moderately rapidly absorbed in both studies. As seen in Tables 1 and 2, T_{max} values across groups within studies and across the single-dose and multiple-dose studies were 4 to 5 hours, with no apparent dose dependency.

As indicated in Table 1, after a single oral dose of PA-824 in Study CL-001, the C_{max} observed ranged from 0.3 ± 0.1 µg/mL (50 mg dose group) to 2.9 ± 0.5 µg/mL (1500 mg dose group), and mean total exposure ($AUC_{(0-\infty)}$) ranged from 7.5 ± 3.9 µg·h/mL (50 mg dose group) to 101.8 ± 25.3 µg·h/mL (1000 mg dose group). Similarly, $AUC_{(0-36)}$ values ranged from 5.5 ± 2.4 µg·h/mL (50 mg dose group) to 73.7 ± 16.5 µg·h/mL (1500 mg dose group).

In both the single-dose and multiple-dose studies, plasma PA-824 levels increased less than dose-proportionally, with an apparent plateauing of bioavailability seen at higher dose levels. In the single-dose study, dose levels above 1000 mg achieved minimal additional PA-824 exposure for both C_{max} and AUC. Mean C_{max}, $AUC_{(0-36)}$, and $AUC_{(0-\infty)}$ values for each of the three highest dose groups (1000, 1250, and 1500 mg) were approximately 2.9 µg/mL, 70 µg·h/mL, and 100 µg·h/mL, respectively. Similarly, in the multiple-dose study, mean C_{max} and AUC values after the first dose at 600 mg and 1000 mg were nearly identical (1.8 vs. 1.9 µg/mL and 31.6 vs. 34.2 µg·h/mL for the 600 mg and 1000 mg dose groups, respectively).

In the 200 mg and 600 mg dose groups examined in the multiple-dose study, steady state was achieved after 5 to 6 days of dosing, and daily dosing for up to 7 days was associated with an approximate PA-824 accumulation ratio of 2. After 7 daily doses, mean steady-state trough (C_{min}), C_{max}, and $AUC_{(0-\tau)}$ values for the 600 mg dose group were 2.1 μg/mL, 3.8 μg/mL, and 70.4 μg•h/mL, respectively. Because dosing in the 1000 mg dose group was halted on Day 5 because of observed increases in serum creatinine, reliable steady-state data are not available for this dose level.

The elimination half-life ($t_{1/2}$) of PA-824 ranged from 11 to 31 hours among the 58 subjects. In Study CL-001, the mean $t_{½}$ ranged from 13.5 to 20 hours across dose groups. The mean $t_{½}$ for the CL-001 study population was approximately 18 hours. In Study CL-002, the mean $t_{½}$ after 7 days of dosing was 16.0 and 15.5 hours in the 200 mg and 600 mg dose groups, respectively. At both an individual- and group-mean level, $t_{½}$ values were not related to dose. These elimination-kinetics data suggest that PA-824 can be administered once daily.

Safety and tolerability. PA-824 was well tolerated at all doses studied, with no serious adverse events occurring in either Study CL-001 or Study CL-002. No systematic or dose-group–related effects on 2-lead cardiac profiles or 12-lead electrocardiogram parameters (e.g., heart rate, QT, QTc) were noted. In addition, no effects were observed on vital signs, such as heart rate, blood pressure, temperature, or respiration. Overall, headache was the most common adverse event, followed by elevated serum creatinine levels, stomach discomfort (nausea, vomiting, flatulence, and/or diarrhea), and back pain. Generally, these adverse events were not noted or they occurred at lower rates among placebo subjects.

PA-824 administration was associated with a reversible elevation in serum creatinine levels. The magnitude of creatinine change from pre-dose values was correlated from subject to subject with the amount of drug exposure (Cmax; AUC) experienced by the subjects. As drug levels declined after dosing was completed, creatinine levels returned to pre-dose values. In the multiple-dose study, minimal to moderate elevations in serum creatinine were observed in the PA-824–treated subjects in the 200 mg and 600 mg dose groups. No individual value exceeded 1.3 mg/dL (200 mg dose group) or 1.4 mg/dL (600 mg dose group), and no absolute value or predosing-to-dosing period change was considered clinically significant. The study site's clinical laboratory normal range for serum creatinine was 0.8 to 1.3 mg/dL for males and 0.6 to 1.0 mg/dL for females. In the 1000 mg dose group (8 males, 0 females), by Day 5 of dosing, serum creatinine levels had risen in five of six PA-824 subjects by an average of 0.28 mg/dL relative to baseline; the highest recorded absolute value was 1.6 mg/dL. Several other individual serum creatinine values were also beyond the upper limit of the normal range. Consequently, dosing was stopped on Day 5. All serum creatinine levels returned to clinically normal levels during the ensuing 7-day washout period in all subjects.

Figure 3 shows the relationship in Study CL-002 between Day 6 trough (C_{min}) PA-824 levels and the corresponding pre-dose to Day 6 changes in creatinine levels for each PA-824 subject (diamonds). Day 6 was approximately steady state in this study. The majority of PA-824–dosed subjects with PA-824 concentrations higher than approximately 1500 ng/mL demonstrated creatinine increases beyond the range seen in placebo subjects (squares). Daily drug and creatinine measurements revealed that

creatinine levels progressively rose as PA-824 accumulated during the 5- to 7-day treatment period and then declined in the post-dose monitoring period (not shown). No consistent pattern of change was observed in blood urea nitrogen levels with treatment or across dose groups. Moreover, subjects with the greatest changes in blood urea nitrogen were not among those with the greatest changes in serum creatinine; the converse was also true.

DISCUSSION

Nonclinical studies of the efficacy of PA-824 indicate its potential for shortening treatment of active TB and providing a novel drug for the treatment of multidrug-resistant and extensively drug-resistant TB. Single- and multiple-dose studies of PA-824 in healthy human subjects indicate that PA-824 is readily absorbed, bioavailable (subdose-proportionally), and well tolerated.

Pharmacokinetic parameters for PA-824 demonstrate oral bioavailability and a half-life consistent with a once-per-day (or less frequent) dosing regimen. In single- and multiple-dose studies, the mean T_{max} across studies was 4 to 5 hours and the $t_{1/2}$ averaged 16 to 20 hours, with steady state reached at 5 to 6 days. Plasma PA-824 levels increased sub-dose proportionally with increasing doses up to 1000 mg. Dose levels above 600 mg achieved minimal additional PA-824 absorption with respect to C_{max} and AUC. The reason(s) behind the subdose proportionality in PK remain to be elucidated definitively but could be due, for example, either to reduced dissolution at relatively high doses of this lipophilic compound or to saturation of absorption mechanisms.

The PA-824 maximal blood levels observed in these studies after a single dose are approximately six-fold to 200-fold higher than MIC values determined in vitro for both

316 drug-sensitive and drug-resistant strains of *M. tb.* These findings suggest that PA-824
317 tablets may demonstrate efficacy in vivo, although efficacy may ultimately be influenced
318 by in vivo protein binding, which has been determined to be on the order of 95% in vitro
319 (data not shown). The avidity of this binding, however, has not been determined.
320 In the two clinical studies reported here, no significant or serious adverse events were
321 observed in the 58 subjects dosed with up to 1000 mg PA-824 for up to 7 days (the
322 multidosing was halted at 5 days at 1000 mg due to increases in serum creatinine—see
323 below). In general, the common adverse events detected to date can be monitored and
324 managed easily and are not likely to preclude patient tolerance of PA-824 for treatment of
325 TB should it ultimately be shown to be safe and effective in pivotal clinical trials.
326 Furthermore, serum creatinine elevation, the one common adverse event that is not
327 monitored as easily in the field, has been shown to be unrelated to human safety when
328 directly examined in a renal effects study (see [cross-reference to companion publication
329 in this issue]).
330 Overall, PA-824 was well tolerated following oral doses up to 1000 mg once daily
331 for up to 5 days and up to 600 mg once daily for up to 7 days. Additionally, it
332 demonstrated oral bioavailability and pharmacokinetic parameters consistent with a once-
333 a-day regimen.
334 The results of these studies, combined with the activity PA-824 demonstrated in
335 vitro against drug-sensitive and drug-resistant *M. tb.* and in a mouse model against drug-
336 sensitive *M. tb.*, support further investigation of this novel compound for the treatment of
337 TB. Additional clinical trials planned for PA-824's clinical development program include
338 drug-drug interaction studies with other anti-TB drugs and antiretroviral agents and a

suite of efficacy studies in TB patients, including a proof-of-concept and dose-finding study to assess extended early bactericidal activity of PA-824 in TB patients. Further studies in the mouse model of TB are planned to explore the activity of PA-824 when it is combined with other current and investigational drugs in novel regimens.

ACKNOWLEDGEMENTS

This work was supported by grants from the Rockefeller Foundation, Development Cooperation Ireland, the Bill and Melinda Gates Foundation, the United States Agency for International Development, and the Dutch Ministry of Foreign Affairs. The authors also wish to thank the staff of MDS Pharma Services and the study participants.

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FIGURE LEGENDS

FIG. 1. Mean plasma concentrations of PA-824, Study CL-001, linear data

Note: Squares = 50 mg; circles = 250 mg; diamonds = 500 mg; triangles = 750 mg; closed circles = 1000 mg; stars = 1250 mg; hashes = 1500 mg PA-824.

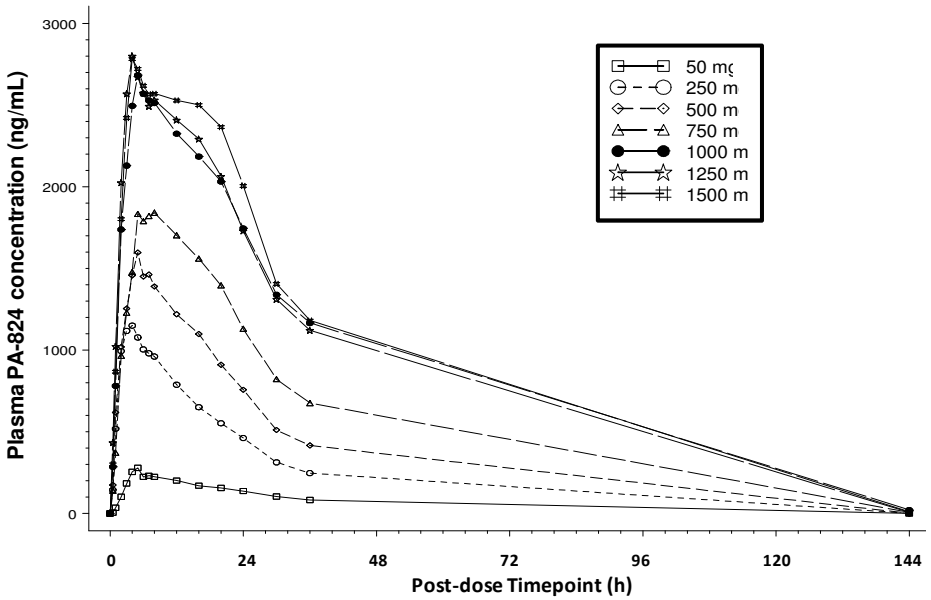
FIG. 2. Mean plasma concentrations of PA-824,* Study CL-002, linear data

Note: Squares = 200 mg/day PA-824; circles = 600 mg/day PA-824; diamonds = 1000 mg/day PA-824.

FIG. 3. Change in serum creatinine from baseline vs. Day 6 C_{min}, Study CL-002

Note: Squares = placebo; diamonds = PA-824.

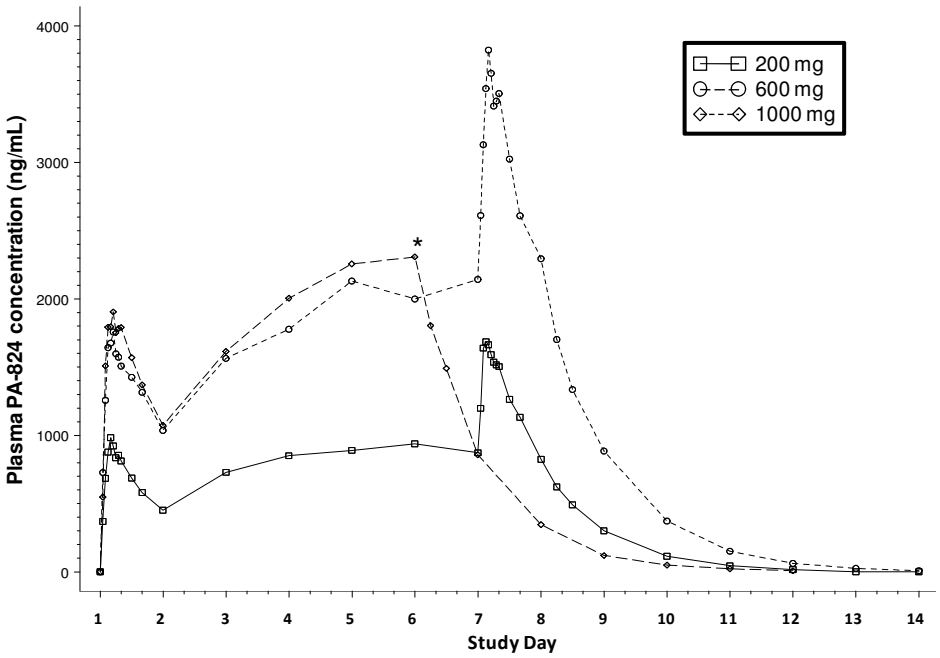
407 **Fig. 1**



408 ***Source: Global Alliance for TB Drug Development***

409

410 **Fig. 2**



*** Dosing stopped for 1000-mg dose level after dosing on Day 5**

Source: Global Alliance for TB Drug Development

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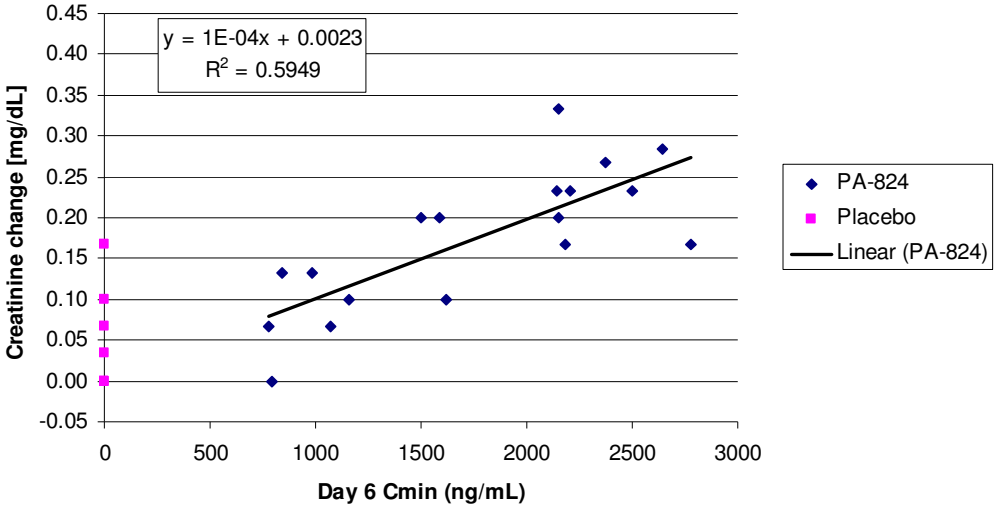
412

413 **Fig. 3**



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416 TABLE 1. Pharmacokinetic parameters for single-dose study (CL-001)

Dose (mg)		C_{max} (µg/mL)	T_{max}* (h)	$t_{½}$ (h)	$AUC_{(0-36)}$ (µg·h/mL)	$AUC_{(0-\infty)}$ (µg·h /mL)	CL/F (L/h)
50 (n=5)	Mean	0.3	5.0	15.2	5.5	7.5	8.47
	SD/range	0.1	(5.0,12.0)	3.04	2.4	3.9	4.67
250 (n=8)	Mean	1.2	4.0	14.0	22.0	27.0	9.5
	SD/range	0.3	(2.0, 5.0)	2.68	4.1	4.3	1.87
500 (n=8)	Mean	1.6	5.0	13.5	33.2	41.5	12.6
	SD/range	0.3	(3.0, 6.0)	1.58	6.6	9.4	3.17
750 (n=8)	Mean	2.0	5.0	16.1	45.3	61.4	13.2
	SD/range	0.5	(2.0,8.0)	4.45	12.8	19.5	3.9
1000 (n=8)	Mean	2.8	5.0	20.0	67.5	101.8	10.4
	SD/range	0.6	(2.0,16.0)	3.32	14.4	25.3	2.59
1250 (n=8)	Mean	2.9	4.0	18.1	69.4	99.2	13.1
	SD/range	0.4	(3.0,12.0)	3.53	11.9	21.0	3.18
1500 (n=8)	Mean	2.9	4.5	15.6	73.7	101.2	15.9
	SD/range	0.5	(3.0,12.0)	3.07	16.5	28.2	4.78

* For T_{max}, median and range (min, max) are presented.

417

418 TABLE 2. Pharmacokinetic parameters for multiple-dose study (CL-002)

Dose (mg)	C_{max} (μg/mL)	T_{max}* (h)	$t_{½}$ (h)	$AUC_{(0-24)}$ (μg·h/mL)	$AUC_{(0-\tau)}$ (μg·h/mL)	CL/F (L/h)
200 mg (n= 8)						
Day 1	1.0 (0.3)	4.1 (2.0,5.1)	18.9 (2.9)	15.6 (3.8)		7.7 (2.3)
Day 7	1.7 (0.3)	4.5 (2.0,8.0)	16.0 (1.6)		30.2 (3.7)	6.7 (.76)
600 mg (n=8)						
Day 1	1.8 (0.4)	5.0 (3.0,5.0)	23.4 (3.9)	31.6 (7.9)		9.9 (3.6)
Day 7	3.8 (0.8)	4.0 (3.0,4.0)	15.5 (2.1)		70.4 (14.3)	8.8 (1.8)
1000 mg (n=8)						
Day 1	1.9 (0.9)	5.0 (3.0,8.0)	21.2 (5.6)	34.2(13.8)		16.6 (6.7)
Day 7	ND	ND	ND		ND	ND

419 *For T_{max}, median and range (min, max) are presented. Other values are arithmetic means (standard
420 deviations). ND = not determined. No Day 7 data are available for the 1000 mg/day dose group because
421 dosing was halted after Day 5.