ZITHROMAX® AZITHROMCYIN

MYCOBACTERIUM AVIUM INTRACELLULARE TREATMENT NDA SUPPLEMENT

Section 3.F and Section 6 Human Pharmacokinetics and Bioavailability

Clinical Pharmacology

Cross Reference from 3.H.1

AZITHROMYCIN MAC TREATMENT NDA

3.H.1 CLINICAL PHARMACOLOGY SUMMARY

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3.H.1 CLINICAL PHARMACOLOGY SUMMARY

3.H.1.A Introduction

The present supplemental New Drug Application is intended to support the addition to the azithromycin product labeling of a new efficacy claim for treatment of disease due to infection by *Mycobacterium avium* Complex (MAC). Azithromycin is already approved for prophylaxis against MAC at a dose of 1200 mg, once per week (NDA -50-730, Approved June 12, 1996). However, it was anticipated that treatment of pre-existing MAC infection might require a somewhat higher dose of azithromycin. The intended dosage is 600 mg azithromycin daily, administered as a single 600 mg tablet in combination with ethambutol at its approved dosage. These tablets were described previously (NDA-50-730). General information on azithromycin pharmacokinetics, tissue distribution, and excretion was presented in earlier submissions and is incorporated by cross-reference.

MAC is primarily a disease of phagocytic cells. Therefore, one goal of the pharmacokinetics program associated with the potential use of azithromycin in the treatment of MAC was to examine the concentrations of azithromycin in human leukocytes following the treatments used in the Phase II/III program. Therefore, this application contains the results of a single pharmacokinetic study (#066-077), which examines the serum and leukocyte concentrations of azithromycin following administration of 250 mg and 600 mg azithromycin per day for 22 days.

MAC most often occurs in patients with a compromised immune system, especially in patients with advanced HIV. Patients being treated for HIV are usually on a variety of anti-HIV drugs, such as protease inhibitors and reverse-transcriptase inhibitors, and other agents used for prevention/treatment of fungal infections or bacterial infections. Azithromycin has little potential to interact with cytochrome P450, including 3A4 [1,2,3] the isozyme responsible for metabolism of many of the agents used for prophylaxis or treatment in HIV-positive patients. However, studies have been performed to examine the potential for azithromycin to cause clinically significant alterations in the pharmacokinetics of some of these agents. This application contains the results of four of these studies. The agents are fluconazole (Study #066-086), trimethoprim/sulfamethoxazole (TMP/SMZ - Study #066-088), indinavir (Study #066-085), and nelfinavir (Study #066-094). The results of studies #066-085 and #066-086 have already been sent to the agency under IND-34,862 ( ), but are included here for the convenience of the reviewers. Other agents (zidovudine, didanosine, rifabutin, efavirenz) are incorporated by cross reference to previously-approved NDAs.

Table 3.H.1.a displays the results of the multiple-dose pharmacokinetics study (#066-077). Table 3.H.1.b displays the results of the pharmacokinetic interaction studies.

The formulations used in these studies are described in Section 6 (Human Pharmacokinetics and Bioavailability Section) of this NDA.

Assay Methods: Concentrations of azithromycin in serum or plasma, urine, tissues, and other matrices were usually determined with an HPLC assay that utilizes electrochemical detection. Some studies also used an HPLC assay with detection by mass spectrometry. The lower limit of quantification (LLOQ) for these assays in serum or plasma was usually 0.010 µg/ml. Although bioassays produce results equivalent to those produced by the HPLC-EC assay, bioassays were not routinely used for serum or plasma concentrations of azithromycin because the HPLC methods are more sensitive. The assays used in specific

studies are appended to the Study Reports in Section 6 (Human Pharmacokinetics and Bioavailability) of this NDA. Assays for other therapeutic agents utilized in interaction studies are described in the assay reports appended to those studies.

3.H.1.B SUMMARY STATEMENTS

As described in the following subsections, the results of these studies of pharmacokinetics and interaction studies in man support the following statements:

Pharmacokinetics/Pharmacodynamics

1. Following oral administration of 600 mg azithromycin per day as a single 600 mg tablet, steady state is approached by day 15. Mean serum steady-state (day 22) values were 0.145 μg/ml for C_0, 0.553 μg/ml for C_{max} and 5.84 μg.hr/ml for AUC_{0-24}. Mean leukocyte (monocytes and neutrophils) concentrations are at least 400-fold those of serum. Steady-state values were 146 μg/ml for C_0, 252 μg/ml for C_{max} and 4760 μg.hr/ml for AUC_{0-24}. The average concentration of azithromycin in leukocytes (AUC_{0-24}/24 hr) was approximately 198 μg/ml. Thus at steady-state, peak leukocyte values are approximately 8 times above and average leukocyte levels 6 times above the MIC90 for MAC of 32 μg/ml. The high concentrations of azithromycin above the MIC90 in leukocytes suggest that this dose regimen should be effective in treating infections due to *Mycobacterium avium* complex.

Interaction Studies

1. Coadministration with 1200 mg azithromycin did not alter the pharmacokinetics of an 800 mg oral dose of fluconazole.

2. Total exposure and half-life of 1200 mg azithromycin were unchanged by coadministration with 800 mg fluconazole. A clinically insignificant decrease in C_{max} (18%) of azithromycin was observed following coadministration of azithromycin with 800 mg fluconazole.

3. Following administration of 160 mg trimethoprim/800 mg sulfamethoxazole for 7 days to healthy subjects, coadministration of 1200 mg azithromycin on the 7^{th} day had no significant effects on peak concentrations or total exposure or urinary excretion of either trimethoprim or sulfamethoxazole.

4. Serum concentrations of azithromycin following administration of a single 1200 mg dose after administration of 160 mg Trimethoprim/800 mg Sulfamethoxazole DS for 7 days were similar to those produced following a 1200 mg dose of azithromycin in other studies.

5. Coadministration of a single dose of 1200 mg azithromycin had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir *TID* for 5 days).

6. Coadministration of 1200 mg azithromycin with steady-state nelfinavir produced an approximately 16% decrease in serum concentrations of nelfinavir and its M8 metabolite.

7. Coadministration of nelfinavir (750 mg TID) at steady state with a single dose of 1200 mg azithromycin increased the AUC of azithromycin by approximately 113% probably due to an alteration of the bioavailability of azithromycin.

Dose rationalization

Efficacy of azithromycin in treatment of infections is related to concentrations in relevant tissues. MAC is essentially a disease of macrophages. Single daily doses of 600 mg oral azithromycin produced an average concentration in leukocytes of 199 μg/ml, a value greater than the concentrations required to inhibit *Mycobacterium avium intracellulare*, suggesting that daily 600 mg oral azithromycin will be effective treatment for infections due to MAC.

3.H.1.C DESCRIPTION/RESULTS OF STUDIES

Pharmacokinetics

Study #066-077 was a two-way, parallel design study that examined the serum and leukocyte concentrations of azithromycin following oral administration of 250 mg or 600 mg doses once daily for 22 days in 14 asymptomatic HIV-seropositive subjects, 7 on each treatment. The 250 mg doses were administered as single tablets (FID #YY-90-071, Lot #ED-G-063-391). The 600 mg doses were administered as single tablets (FID #G00079AA, Lot #ED-G-047-393). On days 1, 8, 15, and 22 serum and buffy coat were collected for 24 hours post-dose. Buffy coat was processed with the LeucoPREP© (Becton Dickinson Labware, Lincoln Park, NJ) process to yield a mixture of mononuclear cells and lymphocytes. Following separation of the mononuclear cells and lymphocytes, they were suspended in saline solution for assay for azithromycin by HPLC with electrochemical detection. The dynamic range of the assay was 0.010 μg/ml to 1.0 μg/ml in serum and in buffy coat. Because the lower limit of quantification for the assay of azithromycin in the saline suspension was approximately 10 ng/ml and the suspensions contained approximately l $2x10^6$and a typical cell volume was approximately 250 fl, concentrations of less than approximately 20 μg/ml in the leukocytes could not be determined with the HPLC-EC assay. Since many samples of leukocytes following administration of 250 mg/day were below quantifiable levels, these samples were reassayed utilizing a newly developed HPLC-MS assay. The HPLC-MS assay had a dynamic range of 0.531 ng/ml to 100 ng/ml.

The predose or trough concentration (C0) of azithromycin just prior to a daily dose was obtained by inspection of the data. The trough concentration on Day 2 was taken as the C24 value following the first dose. Maximum observed serum concentration (C_{max}) was determined by inspection of the data. T_{max} was defined as the time of first occurrence of C_{max}. Area under the serum concentration versus time curve for the interval of predose to 24 hr (AUC_{0-24}) was calculated by the trapezoidal method. Terminal elimination rate (k_{el}) following the last dose was estimated as the least-squares regression of the log-linear terminal phase of the serum concentration-time curve. Terminal half-life (T1/2) = $0.6931/k_{el}$. The approach to steady-state was assessed by the examination of the ratio of $AUC_{0\text{-}24Day\ N}/AUC_{0\text{-}24Day\ 22}$, where N is 1, 8, and 15 days. A similar assessment of C_{max} and C0 was performed. For comparison of the pharmacokinetics following the 250 mg tablets and the 600 mg tablets, values of C0, C_{max}, and AUC_{0-24} following the 600 mg tablet were corrected to a 250 mg basis: adjusted value = value*250/600. Geometric mean values of C0, C_{max}, AUC_{0-24}, and ratios of these parameters are reported. Arithmetic mean values of T_{max} and kel are reported. Harmonic mean values of T1/2 are reported.

Concentrations of azithromycin in leukocytes (monocytes and lymphocytes) were reported as the amount of drug (μg) per ml of approximately 10^6 cells resuspended in saline. In order to estimate concentrations within these cells, the concentration in saline was divided by the cell count to produce the amount of azithromycin per cell. Concentration within the cells was then estimated by dividing the amount of azithromycin in each cell by the average cell volume. Cell volume is approximately 421 femtoliters (fl) per monocyte and 204 fl per lymphocyte. Therefore, the average cell volume (in femtoliters) = 421*fm + 204*fl, where fm and fl are the fractions of monocytes and leukocytes recovered from the LeucoPREP process. fm and fl were estimated from the percentages of monocytes and lymphocytes in blood samples obtained for CBC, assuming that LeucoPREP processing does not alter the relative numbers of monocytes and lymphocytes: fm = %monocytes/(%monocytes + %lymphocytes) and fl = 1 - fm. Cell counts or each leukocyte sample were based on the last preceding CBC determination. C_{max}, T_{max}, AUC_{0-24} and k_{el} for azithromycin in the leukocytes were calculated by the same procedures utilized for serum. Geometric mean values of C_{max}, AUC_{0-24} and the ratio $AUC_{0-24leukocytes}/AUC_{0-24serum}$ are reported. Harmonic mean values for T1/2 are reported. Arithmetic means are reported for all other parameters.

Serum concentrations increased rapidly between days 1 and 8 and to a lesser extent by day 15, but relatively little between days 15 and 22 (AUC_{0-24} ratios of 0.95 [p=0.68] and 0.87 [p=0.22] following 250 mg and 600 mg daily doses), suggesting that steady state concentrations were nearly achieved by day 15. Mean serum steady-state (day 22) values were 0.145 μg/ml for C0, 0.553 μg/ml for C_{max} and 5.84 μg.hr/ml for AUC_{0-24}. Leukocyte concentrations followed a similar pattern with substantial increases between days 1 and 8 and 15, but no further increases between days 15 and 22. Mean leukocyte steady-state values were 146 μg/ml for C0, 252 μg/ml for C_{max} and 4760 μg.hr/ml for AUC_{0-24}. Serum concentrations following administration of 600 mg/day were greater than would have been expected from 250 mg data. The ratio of dose-corrected day 22 $AUC_{0-24(600\ mg)}/AUC_{0-24(250\ mg)}$ was 162% (90% confidence interval (CI) 111% to 231%). The ratio of dose-corrected day 22 C_{max}(600 mg)/C_{max}(250 mg) was 123% (90% CI 83% to 184%). However, no significant changes were found in T_{max} (2.1 hr for 600 mg; 2.7 hr for 250 mg; p= 0.27). There was insufficient serum data following 250 mg doses to permit estimation of k_{el} in most subjects. There was no apparent difference in k_{el} between the doses (600 mg : 0.0082 hr-1 , T1/2 84.5 hr; 250 mg: 0.0075 hr-1, T1/2 92.4 hr; p=0.35). The apparent mean half-life of 84.5 hr following 600 mg doses was similar to or slightly greater than that observed in most other studies.

Leukocyte concentrations were much greater than serum concentrations on all study days. The day 22 mean ratios of leukocyte parameter values to serum parameter values were approximately 773 for C0, 227 for C_{max}, and 571 for AUC_{0-24} following 250 mg daily doses and 955 for C0, 456 for C_{max}, and 816 for AUC_{0-24} following 600 mg daily doses. Mean T_{max} was apparently later in leukocytes than in serum following both 250 mg and 600 mg doses. The apparent harmonic mean half-lives of azithromycin in the leukocytes were 131 hr following the 250 mg doses and 83 hr following the 600 mg doses. The difference may be due to the differences in the sensitivity of the HPLC-MS assay (LLOQ = 0.53 ng/ml) and HPLC-EC assay (LLOQ = 20 ng/ml) which were used for the 250 mg/day and 600 mg/day leukocytes samples, respectively. The HPLC-MS assay permitted quantification of azithromycin in leukocytes in all subjects for 336 hr following 250 mg/day for 22 days. In contrast drug was detected by the HPLC-EC assay in leukocyte preparations for 336 hr in only 2 subjects. Leukocyte concentrations following administration of 600 mg/day were greater than would have been expected from the 250 mg data. The ratio of dose-corrected day 22 leukocyte $AUC_{0-24(600\ mg)}/AUC_{0-24(250\ mg)}$ was 231% (90% CI 148% to 361%). The ratio of dose-corrected day 22 leukocyte $C_{max(600\ mg)}/C_{max(250\ mg)}$ was 248% (90% CI 149% to 414%).

Thus, following oral administration of 250 mg tablets or 600 mg tablets of azithromycin to HIV-seropositive subjects for 22 days, serum concentrations of azithromycin approached steady state by day 15. Leukocyte concentrations were more than 200-times those of serum following doses of 250 mg/day and more than 400-times those of serum following doses of 600 mg/day. to dose. The average concentration of azithromycin in leukocytes ($AUC_{0\text{-}24/24\ hr}$) was approximately 198 μg/ml following doses of 600 mg azithromycin per day, suggesting that this dose should be effective in treating infections due to *Mycobacterium avium* complex.

Interaction Studies

Study #066-086 was an open, randomized, three-way, placebo controlled, crossover study to examine the possible effect of fluconazole and azithromycin on each other's pharmacokinetics. Eighteen healthy male and female volunteers received single doses of 800 mg fluconazole (four 200 mg commercial tablets), 1200 mg azithromycin (two 600 mg commercial tablets), and the combination. Serum was collected for 168 hr post-dose for assay for fluconazole and for 240 hr post-dose for assay for azithromycin. Serum was assayed for azithromycin utilizing HPLC-EC with a dynamic range of 10.4 to 1000 ng/ml. Serum was analyzed for fluconazole utilizing HPLC-UV with a dynamic range 0.05 to 20.0 μg/ml. Maximum observed fluconazole and azithromycin concentrations (C_{max}) were determined by inspection of the data. T_{max} was defined as the time of first occurrence of C_{max}. Area under the change in serum concentration versus time curves (AUC_{last}) were calculated for the interval of predose to the last time at which concentrations of fluconazole or azithromycin were measurable. Terminal elimination rates (k_{el}) were estimated by least-squares regression of the terminal log-linear portion of the serum concentration/time curves. Terminal half-life (T1/2) = $\ln(2)/k_{el}$. Total exposure of fluconazole was estimated as AUC for the interval of predose to infinity. AUC = AUC_{last} + C*last/k_{el}, where C*last is the concentration estimated from the aforementioned regression at the time of the last quantifiable concentration of drug. K_{el} could not be determined for 9 sets of azithromycin data. Therefore, comparison of exposures of azithromycin in the presence and absence of fluconazole was based upon comparisons of AUC_{last}.

Mean concentrations of fluconazole were similar following oral administration with and without azithromycin. Similar geometric mean values were observed for fluconazole when administered with or without azithromycin for C_{max} (22.1 μg/ml and 21.2 μg/ml; ratio = 104%; 90% CI on the ratio of 98% and 111%) and AUC (893 μg.hr/ml and 884 μg.hr/ml; ratio = 101%; 90% CI (CI) 97% and 105%). Mean values were similar in the presence and absence of azithromycin for T_{max} (1.3 hr and 1.4 hr), k_{el} (0.0216 hr-1 and 0.0215 hr-1) and t1/2 (32.1 hr and 32.2 hr). Thus, coadministration with 1200 mg azithromycin did not alter the pharmacokinetics of an 800 mg oral dose of fluconazole.

Mean concentrations of azithromycin were similar following oral administration with and without fluconazole. The mean value of C_{max} following coadministration with fluconazole (0.992 μg/ml) was less than that following administration of azithromycin alone (1.21 μg/ml). The mean ratio $C_{maxFL+AZ}/C_{maxAZ}$ was 0.82 with 90% confidence limits on the ratio of 66% and 102%. Mean values of AUC_{last} were similar (13.1 μg.hr/ml and 12.2 μg.hr/ml; mean ratio = 1.07; 90% CI 94% and 122%). Mean values of T_{max} were similar (2.2 hr and 1.9 hr). Mean values of k_{el} for azithromycin in those subjects for whom this parameter could be assessed were 0.0137 hr-1 (T1/2 50.6 hr; N=14) following coadministration with fluconazole and 0.0131 hr-1 (T1/2 52.9 hr; N=11) following administration of azithromycin alone. Therefore, coadministration with fluconazole did not alter the exposure or elimination characteristics of

azithromycin. However, an insignificant decrease in C_{max} of azithromycin was observed following coadministration of 1200 mg azithromycin with 800 mg fluconazole.

Study #066-088 was an open, randomized, parallel design study with two treatment arms that evaluated the effect of a single 1200 mg dose of azithromycin on the steady-state pharmacokinetics of orally administered trimethoprim (TMP)-sulfamethoxazole (SMZ) DS (160 mg TMP + 800 mg SMZ) QD in healthy volunteers. All subjects were given a daily regimen of 160 mg trimethoprim + 800 mg sulfamethoxazole for 7 days. On day 7, a single 1200 mg dose (two 600 mg tablets) of azithromycin or placebo was administered. Plasma for assay of TMP and SMZ was collected at specified times for the 24 hr period following dosing on days 6 and 7. Urine for assay of TMP and SMZ was collected for the 24 hr period following dosing on days 6 and 7. TMP-SMZ plasma and urine samples were assayed with validated HPLC (Harris Laboratories, Inc., Lincoln, NE). The linear dynamic ranges were 0.05 to 4.0 μg/ml for TMP and 0.5 to 40 μg/ml for SMZ in plasma and 1.0 to 100 μg/ml for both TMP and SMZ in urine. Serum for assay for azithromycin was collected at specified times for up to 120 hr following dosing with azithromycin on day 7. Serum samples were assayed for azithromycin with a validated high performance liquid chromatography method with electrochemical detection (BAS Analytics, West Lafayette, IN). The assay had a linear dynamic range of 0.01 to 1.0 μg/ml.

Maximum observed concentrations (C_{max}) of TMP and SMZ were determined by inspection of the data. T_{max} was defined as the time of first occurrence of C_{max}. Area under the change in serum concentration versus time curves for TMP and SMZ were calculated for the interval of predose to 24 hr (AUC_{24}). Geometric mean values of C_{max}, $AUC_{(0-24)}$, C_{max} ratios, and AUC ratios are reported. Arithmetic means of other parameters are reported. Urine collected for the 24 hr intervals following the morning dosing on days 6 and 7 was analyzed for TMP and SMZ. The total amount of drug excreted in the urine (Du) and renal clearance (CLr), computed as Du/AUC24, were estimated for TMP and SMZ. For azithromycin, the AUC for the interval of predose to 120 hr postdose was estimated by the trapezoidal method (AUC_{120}). Terminal elimination rates (k_{el}) were estimated by least-squares regression of the terminal log-linear portion of the serum concentration/time curves. Terminal half-life (T1/2) = $\ln(2)/k_{el}$. AUC for the interval of predose to infinity was estimated as AUC_{120} + C^*120/k_{el}, where C*120 is the concentration at 120 hr, obtained from the aforementioned regression.

For TMP and SMZ, three trough levels for Days 5, 6, and 7 were evaluated to verify attainment of steady-state. Comparisons of mean trough concentrations between Days 5, 6, and 7 showed no statistically significant differences indicating that steady-state had been reached by Day 5. The mean trough concentrations differed among the three days by less than 1% for TMP with the 90% CI lying between 92.9-108.4. Likewise, for SMZ, the mean trough concentrations differed at most by 8.5% (90%CI: 85.6-105.0).

Three comparisons were analyzed for both TMP and SMZ: Day 6 vs Day 7 within Group A, Day 6 vs Day 7 within Group B, and the difference between Groups A and B. For the purpose of this summary only the comparison between Day 7 and Day 6 within Group A is discussed, since the result in Group B showed no effect in the placebo group as expected. For TMP, the geometric mean ratio for $AUC_{(0-24)}$ for Day 7 to Day 6, for the subjects within Group A was 89.6% (90% CI : 84.2- 95.4). The corresponding geometric mean C_{max} ratio for Day 7 to Day 6, within Group A was 87.5% (90%CI: 79.9-95.8). Thus, there was no clinically significant effect of AZM addition upon the steady-state $AUC_{(0-24)}$ of TMP in subjects being dosed daily with 160 mg TMP + 800 mg SMZ. The other TMP pharmacokinetic parameter arithmetic means for T_{max}, CLr and Du, showed 16% increase,

11% and 20% decrease within group A between Day 7 and Day 6, all statistically, pharmacokinetically and clinically non-significant. For SMZ, the geometric mean ratio for $AUC_{(0-24)}$ on Day 7 to Day 6, for the subjects within Group A was 94.4 % (90% CI : 89.3-99.7). The corresponding geometric mean C_{max} ratio for Day 7 to Day 6, within Group A was 96.6% (90%CI : 87.6-106.6). Thus, there was no effect of AZM addition on the steady-state $AUC_{(0-24)}$ of SMZ in subjects being dosed daily with 160 mg TMP + 800 mg SMZ. The other SMZ pharmacokinetic parameter arithmetic means for T_{max}, CLr and Du, showed 45% decrease, and 25% and 31% decreases within-group A between Day 7 to Day 6, which are not considered to be pharmacokinetically or clinically significant.

Mean AZM serum pharmacokinetic parameters C_{max} (1.3µg/ml), T_{max} (1.9 hr), and $AUC_{0-\infty}$ (11.5 µg.hr/ml) following a single dose of 1200 mg azithromycin in healthy normal subjects previously administered TMP-SMZ DS for 6 days are generally similar to those observed following administration of 1200 mg azithromycin in combination with fluconazole and alone (C_{max} 0.99 µg/ml and 1.21 µg/ml; T_{max} 2.2 hr and 1.9 hr; AUC_{last} 13.1 µg.hr/ml and 12.2 µg.hr/ml) (Study #066-086).

Study #066-085 was an open-label randomized, two-way, placebo-controlled, parallel design study. Subjects received 14 doses of indinavir, 800 mg q8h as two commercial 400 mg tablets. One hour prior to the 13th dose, subjects received either 1200 mg azithromycin (two 600 mg tablets (FID #QC2099) or matching placebo (FID # G00770AA). Pharmacokinetics of indinavir were determined following the 10th (Day 4) and 13th dose (Day 5). Serum samples were assayed for azithromycin and indinavir utilizing HPLC-EC assays. The azithromycin assay had a dynamic range of 10.4 to 1000 ng/ml. The indinavir assay had a dynamic range of 12 to 15,000 ng/ml. Maximum observed concentrations (C_{max}) of indinavir were determined by inspection of the data. T_{max} was defined as the time of first occurrence of C_{max}. Area under the change in serum concentration versus time curves for indinavir were calculated for the interval of predose to 8 hr (AUC_8). Terminal elimination rates (k_{el}) were estimated by least-squares regression of the terminal log-linear portion of the serum concentration/time curves. Terminal half-life (T1/2) = $\ln(2)/k_{el}$. Geometric mean values of C_{max}, AUC, C_{max} ratios, and AUC ratios are reported. Arithmetic means of other parameters are reported. For examination of the effect of azithromycin on the pharmacokinetics of indinavir, values for each parameter on study Day 4 were subtracted from the corresponding values obtained on Day 5. The Day 5 - Day 4 values were compared for the azithromycin and placebo groups utilizing group (2-sample) t-tests. Maximum observed azithromycin concentrations (C_{max}) were determined by inspection of the data. T_{max} was defined as the time of first occurrence of C_{max}. Area under the change in serum concentration versus time curves were calculated for the interval of predose to the last time that azithromycin could be detected (AUC_{last}). The duration of concentrations above the lower limit of quantitation was too short, relative to the estimated half-lives of azithromycin, to permit calculation of terminal phase elimination rates in over half of the subjects. The data from 5 subjects who vomited within 1.1 hr following the doses of indinavir and azithromycin on Day 5 were excluded from analysis. Data from 13 subjects who received azithromycin on Day 5 and 14 subjects who received placebo on Day 5 are included in the data analysis.

Following oral administration of 800 mg indinavir TID for 5 days and 1200 mg azithromycin or placebo on Day 5, concentrations of indinavir were similar on Days 4 and 5 in those subjects who received azithromycin on Day 5 (adjusted geometric mean AUC was 23.1 µg.hr/ml on Day 4, 20.8 µg.hr/ml on Day 5; Mean ratio 90%, 90% CI on ratio 81% to 100%; p=0.09) (adjusted geometric mean C_{max} 10.3 µg/ml on Day 4, 9.88 µg/ml on Day 5; mean ratio 96%, 90% CI on ratio 86% to 108%; p=0.54). These results indicate that co-

administration of azithromycin did not have a significant effect on the pharmacokinetics of indinavir. Mean AUC of indinavir on Day 5 (AUC 21.5 μg.hr/ml) in subjects who received coadministered placebo on Day 5 was 87% (90% CI 78% to 96%) of the value on Day 4 (AUC 24.8 μg.hr/ml) (p = 0.02). Similarly, mean C_{max} in subjects who received placebo on Day 5 (8.52 μg/ml) was 81% (90% CI 72% to 90%) of the value on Day 4 (C_{max} 10.6 μg/ml) (p = 0.003). The changes in C_{max} and AUC following coadministration with placebo were inconsistent with expectations. The Day 5 minus Day 4 differences in the mean values of AUC were not different in subjects who received azithromycin and those who received placebo (mean ratio = 104%, 90% CI on ratio of AUCs 90% to 120%; p = 0.68). The ratio of Day 5 minus Day 4 differences in the mean values of C_{max} in subjects who received azithromycin and those who received placebo was 119% (90% CI on ratio of C_{max} 102% to 139% ; p = 0.074). The mean values for k_{el} did not differ between Days 4 and 5 in subjects who received azithromycin on Day 5 (0.668 hr-1 Day 4, 0.658 hr-1 Day 5; 90% CI on difference -0.040 to 0.022; p = 0.61). Placebo subjects did not have a change in k_{el} between Days 4 and 5 (0.674 hr-1 on Day 4, 0.639 hr-1 on Day 5; 90% CI on difference -0.064 to -0.002 hr-1 ; p = 0.078). No important differences were observed in adjusted mean T_{max} of indinavir between subjects who received azithromycin on Day 5 (0.79 hr on Day 4, 0.71 hr on Day 5) and those who received placebo on Day 5 (0.82 hr on Day 4, 0.96 on Day 5). The results indicate that coadministration of azithromycin has no significant effect on the pharmacokinetics of indinavir. However, unexpected decreases in C_{max} and AUC of indinavir were observed following coadministration with placebo.

Study #066-094 was an open-label, randomized, two-way, two-treatment, crossover design study of the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of nelfinavir (Viracept®) at steady state in normal subjects. The effect of nelfinavir on the pharmacokinetics of azithromycin was also examined. Healthy volunteers received 750 mg TID nelfinavir (250 mg commercial tablets) for 11 days. On Day 9 a single dose of 1200 mg azithromycin (600 mg commercial tablets) was administered. Each subject also received a single dose of 1200 mg azithromycin, either two weeks before a nelfinavir regimen or three weeks after a nelfinavir regimen. Serum samples for assay of nelfinavir and its M8 metabolite were obtained predose on Day 7 and between predose and 8 hours after the first dose on Days 8 and 9. Following extraction from serum by solid phase extraction, the extracts were analyzed for nelfinavir and nelfinavir M8 metabolite LC with MS/MS detection. Serum samples obtained between predose and 168 hr after each dose of azithromycin were assayed for azithromycin utilizing HPLC-EC.

Predose concentrations of nelfinavir decreased between Days 7 (2110 ng/ml) and 8 (1740 ng/ml). However, predose concentrations on Days 8 and 9 (1700 ng/ml) were similar. Statistical examination of the data (ANOVA followed by pairwise comparisons) showed that the difference between Days 7 and 8 was significant (p= 0.03). However, the difference between Days 8 and 9 was not significant (p=0.80). Similarly, predose levels of the nelfinavir M8 metabolite declined between Days 7 (718 ng/ml) and 8 (615 ng/ml) and 9 (582 ng/ml). The difference between these concentrations were not significant (Day 7 vs. Day 8, p = 0.20; Day 8 vs. Day 9, p = 0.68). These results suggest that nelfinavir and M8 concentrations had achieved steady state by the morning dose of Day 8.

AUC_{0-8} for nelfinavir decreased from 17.2 μg.hr/ml following administration alone to 14.6 μg.hr/ml following coadministration with azithromycin. The ratio of Day 9 AUC_{0-8} to Day 8 AUC_{0-8} was 0.85 (90% CI = 78% to 93%; p = 0.006). C_{max} for nelfinavir decreased from 3250 ng/ml on Day 8 to 2930 ng/ml on Day 9 following coadministration with azithromycin. The ratio of Day 9 C_{max} to Day 8 C_{max} was 90% (90% CI 81% to 101%; p = 0.13). T_{max} decreased slightly (3.2 hr vs. 2.6 hr; 90% CI = -0.9 hr to -0.3 hr). AUC_{0-8} for the nelfinavir

M8 metabolite following administration alone decreased from 6.30 μg.hr/ml to 5.27 μg.hr/ml following coadministration with azithromycin. The ratio of Day 9 AUC_{0-8} to Day 8 AUC_{0-8} was 84% (90% CI 74% to 95%). C_{max} for nelfinavir decreased from 1240 ng/ml on Day 8 to 1140 ng/ml on Day 9 following coadministration with azithromycin. The ratio of Day 9 C_{max} to Day 8 C_{max} was 92% (90% CI 80% to 104%). T_{max} was little changed (3.1 hr vs. 3.7 hr; 90% CI -1.5 to 0.3 hr). The results suggest that coadministration of azithromycin is associated with a small (~16%) decrease in exposure to nelfinavir and nelfinavir M8 metabolite. While statistically significant, this change may not be clinically significant.

Mean $AUC_{0-\infty}$ for azithromycin increased by 112% (90% CI = 180% to 250%, p = 0.0000) from 11.5 μg.hr/ml to 24.5 μg.hr/ml following coadministration with nelfinavir. Mean C_{max} increased by 136% (90% CI = 177% to 315%; p = 0.0003) from 888 ng/ml to 2100 ng/ml following coadministration with nelfinavir. T_{max} (3.0 hr vs. 2.3 hr; 90% CI = -1.5 hr to 0.1 hr; p = 0.16) and T1/2 (54.3 hr following coadministration with placebo and 51.3 hr following coadministration with nelfinavir; 90% CI = -6.9 hr to 0.8 hr; p = 0.18) were unchanged. The large increase in AUC and C_{max} is probably due to a large change in bioavailability, not a change in elimination characteristics. Azithromycin bioavailability is limited by both absorption at the intestinal wall and by first-pass elimination. It is likely that the effect of nelfinavir on the bioavailability of azithromycin occurs during the process of absorption at the intestinal wall, perhaps through inhibition of azithromycin first pass elimination at the intestinal wall.

3.H.1.D Summary and Conclusions

Pharmacokinetics

Following oral administration of 600 mg azithromycin per day as a single 600 mg tablet, steady state is approached by Day 15. Mean serum steady-state (Day 22) values were 0.145 μg/ml for C0, 0.553 μg/ml for C_{max} and 5.84 μg.hr/ml for AUC_{0-24}. Mean leukocyte steady-state values were 146 μg/ml for C0, 252 μg/ml for C_{max} and 4763 μg.hr/ml for AUC_{0-24}. Following oral administration of 600 mg azithromycin per day, concentrations in leukocytes (monocytes and neutrophils) are at least 400-fold those of serum. The mean leukocyte C0 value of 146 μg/ml and the average concentration of azithromycin in leukocytes ($AUC_{24/24\ hr}$) of approximately 198 μg/ml following doses of 600 mg azithromycin per day for 22 days are greater than the MIC90s reported for *Mycobacterium avium* complex, suggesting that this dose should be effective in treating infections due to *Mycobacterium avium* complex.

Interaction Studies

Coadministration with 1200 mg azithromycin did not alter the pharmacokinetics of an 800 mg oral dose of fluconazole. The 90% confidence limits on the ratio $C_{maxFL+AZ}/C_{maxFl}$ were 98% and 111%. The 90% confidence limits on the ratio AUC_{FL+AZ}/AUC_{FL} were 97% and 105%. Total exposure and half-life of azithromycin were unchanged by coadministration with fluconazole. The 90% confidence limits on the AUC_{FL+AZ}/AUC_{AZ} were 94% and 122%. Mean values of T_{max} were similar (2.2 hr and 1.9 hr). Mean values of k_{el} for azithromycin in those subjects for whom this parameter could be assessed were 0.0137 hr-1 (T1/2 50.6 hr; N=14) following coadministration with fluconazole and 0.0131 hr-1 (T1/2 52.9 hr; N=11) following administration of azithromycin alone. Therefore, coadministration with fluconazole did not alter the exposure or elimination characteristics of azithromycin. However, an insignificant decrease in C_{max} of azithromycin was observed following coadministration of

1200 mg azithromycin with 800 mg fluconazole. The mean ratio $C_{maxFL+AZ}/C_{maxAZ}$ was 82% with 90% confidence limits on the ratio of 66% and 102%.

Following Administration of 160 mg Trimethoprim/800 mg Sulfamethoxazole (TMP/SMZ) for 7 days and azithromycin on the 7th day to healthy subjects, the confidence bounds on the C_{max} and AUC ratios comparing TMP levels following administration with placebo and with azithromycin all fell within the 80% to 125% guidelines for bioequivalence. Also, the confidence bounds on the ratios comparing TMP levels following administration with placebo and with azithromycin all fell within the 80% to 125% guidelines for bioequivalence. The difference between the within-treatment changes in SMZ C_{max} for the placebo group and azithromycin group was 10% (90% CI 78% and 103%). Thus, azithromycin had no significant effects on peak concentrations or total exposure of either TMP or SMZ. Other TMP and SMZ pharmacokinetic parameters (T_{max}, CLr), showed only minor differences between the combination of TMP-SMZ with AZM and TMP-SMZ with placebo. Mean AZM serum pharmacokinetic parameters C_{max} (1.3 µg/ml), T_{max} (1.9 hr), and $AUC_{0-\infty}$ (11.5 µg.hr/ml) following a single dose of 1200 mg azithromycin in healthy normal subjects previously administered TMP-SMZ for 6 days are generally similar to those observed following administration of 1200 mg azithromycin in other studies.

Coadministration of a single dose of 1200 mg azithromycin has no significant effect on the pharmacokinetics of indinavir (800 mg indinavir TID for 5 days). Following oral administration of 800 mg indinavir TID for 5 days and 1200 mg azithromycin or placebo on day 5, concentrations of indinavir were similar on days 4 and 5 in those subjects who received azithromycin on day 5. The mean ratio of adjusted AUC values comparing concentrations following administration of indinavir alone and with azithromycin was 90% (90% CI on ratio 81% to 100%; p=0.09). The mean ratio of adjusted C_{max} values was 96% (90% CI on ratio 86% to 108%; p=0.54). These results indicate that coadministration of azithromycin did not have a significant effect on the pharmacokinetics of indinavir. However, unexpected decreases in C_{max} (19%) and AUC (13%) of indinavir were observed following coadministration with placebo. The mean ratio of adjusted AUC values comparing concentrations following administration of indinavir alone and with coadministered placebo on day 5 was 87% (90% CI 78% to 96%; p = 0.02). Similarly, mean C_{max} in subjects who received placebo on day 5 was 81% (90% CI 72% to 90%; p = 0.003) of the value on day 4.

Coadministration of 1200 mg azithromycin with steady-state nelfinavir (750 mg TID for 8 days) produced a small (~16%) decrease in serum concentrations of nelfinavir and its M8 metabolite. The mean ratio of nelfinavir AUC_{0-8} for nelfinavir administered with azithromycin to AUC_{0-8} for nelfinavir administered alone was 84% (90% CI = 78% to 93%; p = 0.006). The corresponding ratio for C_{max} was 90% (90% CI = 81% to 101%; p = 0.13). The mean ratio of nelfinavir M8 metabolite AUC_{0-8} for nelfinavir administered with azithromycin to AUC_{0-8} for nelfinavir administered alone was 84% (90% CI = 74% to 95%). The C_{max} ratio was 92% (90% CI = 80% to 104%). The results suggest that coadministration of azithromycin is associated with a small (~16%) decrease in exposure to nelfinavir and nelfinavir M8 metabolite. While statistically significant, this change may not be clinically significant.

Coadministration of nelfinavir at steady state (750 mg TID for 8 days) with a single dose of 1200 mg azithromycin increased the serum concentrations of azithromycin. The mean ratio for azithromycin $AUC_{0-\infty}$ following administration with nelfinavir to the $AUC_{0-\infty}$ following administration of azithromycin alone was 212% (90% CI = 180% to 250%, p = 0.0000). The corresponding ratio for mean C_{max} was 236% (90% CI = 177% to 315%; p = 0.0003). T1/2 was unchanged (54.3 hr following coadministration with placebo and 51.3 hr following

coadministration with nelfinavir; 90% CI = -6.9 hr to 0.8 hr; p = 0.18). The large increase in azithromycin AUC and C_{max} is probably due to a large change in bioavailability, not a change in elimination characteristics.

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Table 3.H.1.a.
Results of Clinical Pharmacology Studies: Pharmacokinetics Study

Protocol Number (Country)	Study Objective	Study Design	Number of Subjects enrolled/ Completed	Treatment	Mean Parameter Value (CV%) C_0 (µg/ml)	Cmax (µg/ml)[a]	Tmax (hr)	AUC_{0-24}[a] (µg.hr/ml)	k_{el} (hr^{-1})
#066-077 (USA)	Multiple dose Pharmacokinetics; Concentration in leukocytes	Open, 2-way, randomized, parallel design			PLASMA				
			7/7	250 mg/day for 1 day[b]	0.015 (27)	0.107 (60)	3.9 (95)	0.655 (50)	-
			7/7	250 mg/day for 8 days	0.024 (38)	0.175 (30)	2.6 (19)	1.34 (34)	-
			7/7	250 mg/day for 15 days	0.032 (63)	0.145 (58)	2.9 (38)	1.44 (49)	-
			7/7	250 mg/day for 22 days	0.033 (46)	0.187 (57)	2.7 (30)	1.51 (49)	0.00750[c] (24)
					LEUKOCYTES				
			7/7	250 mg/day for 22 days	27.4 (49)	42.4 (58)	6.9 (72)	860 (51)	0.00528 (39)

Table 3.H.1.a. continued
Results of Clinical Pharmacology Studies: Pharmacokinetics Study

Protocol Number (Country)	Study Objective	Study Design	Number of Subjects enrolled/ Completed	Treatment	Mean Parameter Value (CV%) C_0 (µg/ml)	Cmax (µg/ml)[a]	Tmax (hr)	AUC_{0-24}[a] (µg.hr/ml)	k_{el} (hr^{-1})
#066-077 (USA)	Multiple dose Pharmacokinetics; Concentration in leukocytes	Open, 2-way, randomized, parallel design			PLASMA				
			7/7	600 mg/day for 1 day[b]	0.039 (36)	0.329 (25)	2.0 (50)	2.37 (19)	-
			7/7	600 mg/day for 8 days	0.094 (45)	0.528 (47)	2.3 (43)	4.41 (33)	-
			7/7	600 mg/day for 15 days	0.127 (35)	0.462 (43)	2.3 (35)	5.09 (37)	-
			7/7	600 mg/day for 22 days	0.145 (26)	0.553 (18)	2.1 (52)	5.84 (25)	0.00820 (10)
					LEUKOCYTES				
			7/7	600 mg/day for 22 days	146 (33)	252 (49)	10.9 (28)	4763 (42)	0.00837 (37)

[a] Geometric means
[b] Day 2 for C_0
[c] N = 2

Table 3.H.1.b.
Results of Clinical Pharmacology Studies: Interaction Studies

Protocol Number (Country)	Study Objective	Study Design	Number of Subjects enrolled/ Completed	Treatment	Sample Day	Drug Assayed[a]	Mean Parameter Value (CV%)[b] Cmax (µg/ml)	Tmax (hr)	AUC[Interval] (µg.hr/ml)	k_{el} (hr^{-1})
#066-085 (USA)	Effect of azithromycin on pharmacokinetics of indinavir	Open, randomized, two-way, placebo-controlled, parallel design	18/13	IND: 14 doses of 800 mg, t.i.d.	4	IND	10.3 (21)	0.79 (28)	23.1[8] (34)	0.668 (9)
				AZM: 1200 mg 1 hr before 13th dose.	5	IND	9.88 (18)	0.71 (24)	20.8 (27)	0.659 (8)
			14/14	IND: 14 doses of 800 mg, t.i.d.	4	IND	10.6 (17)	0.82 (22)	24.8 (18)	0.674 (8)
				PBO: 1 hr before 13th dose.	5	IND	8.52 (23)	0.96 (40)	21.5 (17)	0.639 (15)
			18/13	IND: 14 doses of 800 mg, t.i.d. AZM: 1200 mg 1 hr before 13th dose.	5	AZM	1.35 (28)	1.88 (36)	13.5[inf] (21)	0.0174 (15)

Table 3.H.1.b. continued
Results of Clinical Pharmacology Studies: Interaction Studies

Protocol Number (Country)	Study Objective	Study Design	Number of Subjects enrolled/ Completed	Treatment	Sample Day	Drug Assayed[a]	Mean Parameter Value (CV%)[b] Cmax (ng/ml)	Tmax (hr)	AUC[Interval] (µg.hr/ml)	k_{el} (hr^{-1})
#066-086 (USA)	Effect of azithromycin and fluconazole on each other's pharmacokinetics	Open, randomized, three-way, placebo controlled crossover	18/18	FLU: 800 mg plus PBO.	1	FLU	21.2 (19)	1.4 (44)	884[inf] (18)	0.0215 (21)
			18/18	FLU: 800 mg plus AZM: 1200 mg	1	FLU	22.1 (21)	1.3 (45)	893 (19)	0.0216 (20)
			18/18	AZM: 1200 mg plus PBO.	1	AZM	1.21 (32)	1.9 (32)	12.2[last] (23)	0.0131 (23)
			18/18	AZM: 1200 mg plus FLU: 800 mg.	1	AZM	0.992 (41)	2.2 (36)	13.1 (39)	0.0137 (34)

Table 3.H.1.b. continued
Results of Clinical Pharmacology Studies: Interaction Studies

Protocol Number (Country)	Study Objective	Study Design	Number of Subjects enrolled/ Completed	Treatment	Sample Day	Drug Assayed[a]	Mean Parameter Value (CV%)[b] Cmax (µg/ml)	Tmax (hr)	AUC[Interval] (µg.hr/ml)	CLr (ml/min)
#066-088 (USA)	Effect of azithromycin on pharmacokinetics of trimethoprim/ sulfamethoxazole	Open, randomized, placebo-controlled, parallel design	12/12	TMP: 160 mg qd for 7 days; SMZ:	6	TMP	2.22 (19)	1.8 (50)	27.1[24] (23)	50.7 (43)
				800 mg qd for 7 days; PBO on day 7	7	TMP	2.3 (20)	1.7 (53)	27.9 (22)	45.7 (47)
			12/12	TMP: 160 mg qd for 7 days; SMZ:	6	TMP	2.3 (20)	1.6 (63)	29.4 (22)	46.9 (35)
				800 mg qd for 7 days; AZM: 1200 mg on day 7	7	TMP	2 (23)	1.8 (45)	25.8 (25)	41.8 (41)
			12/12	TMP: 160 mg qd for 7 days; SMZ:	6	SMZ	60.9 (19)	3.6 (78)	777[24] (21)	2.46 (46)
				800 mg qd for 7 days; PBO on day 7	7	SMZ	65.7 (19)	2.4 (46)	767 (25)	2.81 (52)
			12/12	TMP: 160 mg qd for 7 days; SMZ:	6	SMZ	63.7 (20)	2.6 (61)	737 (17)	3.16 (41)
				800 mg qd for 7 days; AZM: 1200 mg on day 7	7	SMZ	61.9 (12)	1.4 (36)	696 (15)	2.38 (49)

Table 3.H.1.b. continued
Results of Clinical Pharmacology Studies: Interaction Studies

Protocol Number (Country)	Study Objective	Study Design	Number of Subjects enrolled/ Completed	Treatment	Sample Day	Drug Assayed[a]	Mean Parameter Value (CV%)[b] Cmax (µg/ml)	Tmax (hr)	AUC[Interval] (µg.hr/ml)	k_{el} (hr^{-1})
#066-088 (USA)	Effect of azithromycin on pharmacokinetics of trimethoprim/ sulfamethoxazole	Open, randomized, placebo-controlled, parallel design	12/12	TMP: 160 mg qd for 7 days; SMZ: 800 mg qd for 7 days; AZM: 1200 mg on day 7	7	AZM	1.3 (24)	1.9 (15)	11.5[inf] (30)	0.0177 (9)

Table 3.H.1.b. continued
Results of Clinical Pharmacology Studies: Interaction Studies

Protocol Number (Country)	Study Objective	Study Design	Number of Subjects enrolled/ Completed	Treatment	Sample Day	Drug Assayed[a]	Mean Parameter Value (CV%)[b] Cmax (µg/ml)	Tmax (hr)	AUC[Interval] (ug.hr/ml)	k_{el} (hr^{-1})
#066-094 (USA)	Effect of azithromycin and nelfinavir on each other's pharmacokinetics	Open, randomized, two-way, two-treatment, crossover design	12/12	NLF: 750 mg t.i.d. for 9 days;	9	NLF	3.25 (29)	3.2 (28)	17.2[8] (33)	-
			12/12	AZM: 1200 mg on Day 10	10	NLF	2.93 (27)	2.6 (31)	14.6 (28)	-
			12/12	NLF: 750 mg t.i.d. for 9 days;	9	M8	1.24 (26)	3.7 (38)	6.30[8] (29)	-
			12/12	AZM: 1200 mg on Day 10	10	M8	1.14 (30)	3.1 (45)	5.27 (28)	-
			12/12	AZM: 1200 mg	1	AZM	0.888 (55)	3.0 (28)	11.5[inf] (31)	0.0130 (15)
			12/12	NLF: 750 mg t.i.d. for 9 days; AZM: 1200 mg on Day 10	10	AZM	2.10 (24)	2.3 (39)	24.5 (20)	0.0137 (12)

[a] AZM = azithromycin; IND = indinavir; FLU = fluconazole; TMP = trimethoprim; SMZ = sulfamethoxazole; NLF = nelfinavir; M8 = M8 metabolite of NLF; PBO = placebo.
[b] Geometric mean for Cmax and AUCs.