INTRODUCTION

Onchocerciasis (river blindness) is a debilitating infection that is caused by the filarial nematode Onchocerca volvulus. Thirty-seven million individuals are thought to be infected with O. volvulus; more than 99% of whom reside in 30 endemic countries in West and Central Africa, with the remainder found in Latin America and the Arabian Peninsula.1–3 The parasite is transmitted to humans by vector blackflies of the genus Simulium whose larvae develop in fast-flowing, well-oxygenated rivers and streams. Infective larvae are transmitted to the human host during a blood meal and typically mature to the human host after 1 year into macrofilariae, which can live inside the host for up to 14 years and release millions of microfilariae.4–6 The pathology that is associated with onchocerciasis is primarily caused by the accumulation of dead microfilariae in the skin and eyes; clinical manifestations include visual impairment, in some cases permanent blindness, and onchocercal skin disease, which is associated with severe itching, dermatitis, and depigmentation.

Moxidectin is a macrocyclic lactone drug derived from the actinomycete Streptomyces cyanogriseus spp. noncyanogenus that is currently being developed in collaboration with the World Health Organization for the treatment of onchocerciasis in humans. The drug was initially developed as a veterinary product for the treatment of canine heartworm and for the treatment of internal and external parasites in cattle, sheep, deer, and horses.3 Studies have indicated that moxidectin may exert its antiparasitic action by binding to glutamate-gated chloride channels, leading to hyperpolarization of muscle and nerves, and ultimately to paralysis and parasite death.6,7 Moxidectin also shows activity at the gamma-aminobutyric acid (GABA) receptor complex, where it acts as an agonist and may stimulate the binding of the neurotransmitter GABA that leads to parasite death.8

It is important that human safety and pharmacokinetic (PK) parameters are fully examined for moxidectin. The first-in-man (FIM) study in which single moxidectin doses of 3, 9, 18, or 36 mg were administered to healthy volunteers, assessed the safety, tolerability, and initial PK of an orally administered liquid formulation in both the fed and fasting state.9 Moxidectin was generally well tolerated, the peak plasma concentration (C max ) and the total area under the concentration-time curve (AUC) were linear and dose-proportional, the apparent volume of distribution (V z/F) was large (2,080–3,549 L), and the t ½ was long (485–842 h). The PK parameters and safety of moxidectin was confirmed in a further study in which healthy subjects received moxidectin in either a liquid or tablet formulation.9 Administration of moxidectin as a tablet reduced C max and AUC by 22% compared with administration of the liquid formulation, with a delay in time to maximal plasma concentration (t max ) of ~1 hour, as would be anticipated for a drug with low solubility, such as moxidectin.

The FIM study indicated that consumption of food might delay and increase the absorption of moxidectin as the t max and AUC were significantly higher in the fed cohort compared with the fasting cohort in a small number of subjects.5 Moxidectin has low solubility in water. Administration with high-fat meals can potentially increase bioavailability caused by increased solubilization of the drug in the intestinal lumen.10 Studies in a rat model have shown increased absorption of DDT after a high-fat meal, presumably caused by binding of the DDT molecule to triglyceride-rich lipoproteins, which assemble in the gut after a high-fat meal and are subsequently absorbed by the lymph.11 The currently intended field of use of moxidectin is community-directed treatment of the eligible population in areas of O. volvulus transmission. Adherence to instructions regarding consumption in the fasted or fed state cannot be expected and consequently it is important that the effects of food on the bioavailability of moxidectin are thoroughly evaluated to assess potential implications for efficacy and safety.

MATERIALS AND METHODS

Ethics and consent. The study protocol was reviewed and approved by CPP Ouest VI, CHU Cavale Blanche (Brest, France) and was carried out in accordance with the ethical principles set out in the Declaration of Helsinki, and the good clinical practice guidelines established by the International
Conference on Harmonisation. All subjects provided informed written consent for participation in the study.

**Subjects.** Inclusion criteria required subjects to be healthy (determined by the investigator on the basis of medical history, physical examination, clinical laboratory test results, vital signs measurements, and 12-lead electrocardiogram [ECG] findings); to be men or women of non-childbearing potential; to be 18–50 years of age at the time of screening; to have a body mass index of 18–30 kg/m² and a body weight of at least 50 kg; to be non-smokers or smokers of < 10 cigarettes per day; and to have alanine aminotransferase, aspartate aminotransferase, and creatinine levels below the upper limit of normal at the time of screening. Exclusion criteria included presentation of any of the following: significant cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrinological, immunological, dermatological, hematological, neurological, or psychiatric disease; acute disease, including nausea and vomiting, within 7 days of study Day 1; any surgical or medical condition that could interfere with the absorption, distribution, metabolism, or excretion of moxidectin; a positive urine drug screen or positive test results for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.

**Study design.** This study was a single-dose, randomized, open-label, parallel-group, inpatient/outpatient study conducted in healthy subjects enrolled at one investigational center in France. All subjects were included in a pre-dose screening evaluation (carried out up to 3 weeks before the administration of moxidectin), a 48-h inpatient period, and an outpatient follow-up period for safety and PK for up to 90 days after dosing. Subjects were randomized to receive a single oral dose of moxidectin in tablet form (8 mg) administered on Day 1 with 240 mL of room temperature water under fasting conditions (defined as an overnight fast of at least 10 h) or fed conditions (defined as an overnight fast of at least 10 h followed by a U.S. Food and Drug Administration-recommended high-fat breakfast; moxidectin was administered to subjects in the fed state within 5 minutes of consumption of the breakfast).

**Analysis of PK parameters.** Serial blood samples were collected for ~90 days after dosing. The concentrations of moxidectin present in the plasma were determined using a validated high-performance liquid chromatography with a fluorescence detection method as previously described. The range of quantification was 0.08–120 ng/mL and abamectin was used as an internal standard. The inter-day accuracy (mean bias) and precision (coefficient of variation [%]) for moxidectin concentrations in plasma were < 6.4% and 13.1%, respectively. The mean recovery of moxidectin from plasma samples measured at the four quality control levels was 84.6%. No potential interference was detected from six different lots of plasma.

The plasma concentration-versus-time data following oral administration of moxidectin were determined using non-compartmental methods (WinNonlin, version 5.1.1, Pharsight, Sunnyvale, CA). The Cₓₙ and tₓₙ of moxidectin were determined directly from the observed plasma concentration data. The terminal-phase disposition rate constant (λz) was estimated by a log linear regression of the terminal monoexponential portion of the observed plasma concentrations. The t₁/₂ was calculated as 0.693/λz. The AUC at time T (AUCₜ), truncated at the last measurable concentration at time T (Cₜ), was calculated using the trapezoidal rule during the ascending portion of the curve and the log trapezoidal rule during the descending portion of the curve. The AUC was then estimated from zero to infinity as $AUC = AUC_T + λ_0$. The apparent oral dose clearance (CL) adjusted for bioavailability (F) (CL/F) was calculated as a ratio of moxidectin dose to AUC. The apparent volume of distribution based on the terminal phase (Vₓₙ) adjusted for bioavailability (Vₓₙ/F) was estimated as the ratio of CL/F to λz.

**Analysis of pharmacodynamic parameters.** The pharmacodynamic relationship between treatment with moxidectin and the Q wave-T wave (QT) interval in an ECG was investigated graphically using plots that showed the time-course of moxidectin and QT correction (QTC), based on Fridericia’s formula (QTCF) and a population-specific QT correction (QTCN) formula. Parallel groups were pooled for the QT evaluation.

**Safety.** The investigator recorded the frequency and severity of all adverse events (AEs), and provided opinion on the relationship of the AEs to the study drug.

**Statistical analyses.** Summary statistics were calculated for the PK parameters. To test for differences between the fed and fasting results, an analysis of variance on log-transformed parameters with fasting/fed treatment as a fixed effect was performed. If no difference in Cₓₙ and AUC was found then two one-sided t test procedures were carried out for Cₓₙ and AUC using 90% confidence intervals about the geometric mean ratio of the recorded PK measure of moxidectin in the fed group and the recorded PK measure of moxidectin in the fasting group to assess adherence to bioequivalence.

**RESULTS**

**Subject disposition and demographics.** The demographic and baseline characteristics of subjects are shown in Table 1. Fifty-four eligible male subjects were enrolled in the study and were randomized to receive moxidectin (8 mg) in the fasted state (N = 27) or in the fed state (N = 27). Fifty-three subjects completed the study and were included in the PK analyses. One subject withdrew from the fed cohort on study Day 4.

**Table 1**

| Characteristic | Fasted (N = 27) | Fed (N = 27) | Total (N = 54) |
|---------------|----------------|-------------|---------------|
| Age (years)   | 30.4 (9.5)     | 30.9 (10.7) | 30.7 (10.0)   |
| Mean (SD)     | 19.0–50.0      | 19.0–50.0   | 19.0–50.0     |
| Range         |                |             |               |
| Sex, n (%)    | 27 (100)       | 27 (100)    | 54 (100)      |
| Male          |                |             |               |
| Female        |                |             |               |
| Race, n (%)   | 26 (96.3)      | 26 (96.3)   | 52 (96.3)     |
| White         |                | 1 (3.7)     | 1 (1.9)       |
| Black or African |         |             |               |
| American      |                |             |               |
| Mixed race    | 1 (3.7)        | 0           | 1 (1.9)       |
| Baseline height (cm) | 179.9 (7.6) | 174.9 (6.5) | 177.4 (7.4)  |
| Mean (SD)     | 163.0–194.0    | 160.0–189.0 | 160.0–194.0   |
| Range         |                |             |               |
| Baseline weight (kg) | 75.7 (12.0) | 70.7 (9.5)  | 73.2 (11.0)   |
| Mean (SD)     | 58.0–106.6     | 56.5–89.2   | 56.5–106.0    |
| Range         |                |             |               |
| BMI (kg/m²)   | 23.3 (2.6)     | 23.1 (2.4)  | 23.2 (2.5)    |
| Mean (SD)     | 19.9–29.9      | 18.0–28.4   | 18.0–29.9     |

*BMI = body mass index, calculated as weight (kg)/(height [m]²); SD = standard deviation.
Concentration measurements for this subject have been included in the summary of concentrations, but corresponding PK parameters could not be calculated and have not been included in the summary of PK parameters. All subjects were included in the safety analyses.

**PK.** The mean concentration-time profiles after administration of single oral doses of moxidectin in the fasting and fed states are shown in Figure 1. After administration of moxidectin to subjects in the fed cohort, the mean C\text{max} increased by 34% (P = 0.001), t\text{max} was delayed by 43% (1.6 h; P < 0.05), AUC was increased by 44% (P < 0.05), CL/F decreased by 35% (P = 0.0009), and V\text{z/F} decreased by 40% (P = 0.0003) when compared with fasting subjects (Table 2).

**Safety.** Thirty-three subjects (61.1%) experienced at least one AE during the study and of these, 29 (53.7%) experienced treatment-emergent AEs (TEAEs): 15 (55.6%) in the fasted cohort and 14 (51.9%) in the fed cohort. Eleven of these 29 subjects experienced TEAEs that were considered by the investigator to be drug related, all of which were mild in intensity. The most commonly reported drug-related TEAEs (defined as ≥5% of subjects in either the fed or fasted cohorts) were headache (three [11.1%] subjects in the fasted cohort), flatulence (two [7.4%] subjects in each of the fasted and fed cohorts), and asthenia (two [7.4%] subjects in the fed cohort). One subject withdrew from the study for personal reasons; no serious AEs (SAEs) were reported during the study. There were no clinically important changes in laboratory evaluations, vital signs, or ECGs.

**Pharmacodynamics.** No statistically significant increases in QTc or an upper bound greater than 10 ms were reported for either QTcN or QTcF at any time point (Table 3). At 1-hour and 2-hour time points, both QTcN and QTcF showed a statistically significant decrease in QTc.

**DISCUSSION**

This open-label, randomized, single-dose, parallel-group, inpatient/outpatient study in 54 healthy male subjects was performed to assess the relative bioavailability of moxidectin administered during the fasting state or after consumption of a high-fat meal, and to determine the safety and tolerability of the drug.

The PK parameters reported here are generally consistent with those observed in the FIM study of the liquid formulation of moxidectin that was conducted in 37 healthy subjects in the fasted state or after consumption of a high-fat meal, which showed that in the fed state, administration of 9 and 36 mg of liquid moxidectin exhibited a mean AUC that was 33% and 64% higher, respectively, compared with administration of moxidectin during the fasting state, with no corresponding increase in C\text{max}. Consistent with these observations, mean AUC was 44% higher in this study of moxidectin at a dose of 8 mg in individuals who were fed a high-fat meal compared with those in the fasting state. However, in contrast to the previous study, the mean C\text{max} was 34% higher in the subjects who received moxidectin with food, compared with those subjects who received moxidectin while fasting. This higher C\text{max} is probably a result of the slower absorption of moxidectin in tablet form compared with the liquid formulation (t\text{max} of 3.2 h versus 2.3 h, respectively), allowing improved bioavailability as a result of food administration to become more evident.

The simultaneous lower values in mean observed CL/F and V\text{z/F} (35% and 40%, respectively) in fed subjects suggest that consumption of food results in a change in drug bioavailability rather than a change in intrinsic clearance. The reported increase in bioavailability could be a result of inhibition of efflux transporters in the intestine or because of increased solubilization of the drug in the intestinal lumen.

---

**Table 2**

Moxidectin pharmacokinetics in healthy subjects after single 8-mg doses (mean [SD])

|          | C\text{max} (ng/mL) | t\text{max} (h) | λ\text{z} (h) | t\text{½} (h) | AUC (ng.h/mL) | CL/F (L/h) | V\text{z/F} (L) |
|----------|----------------------|-----------------|--------------|-------------|--------------|------------|--------------|
| Fasted (N = 27) | 58.9 (12.5) | 3.7 (1.5) | 0.00107 (0.00061) | 784 (347) | 3387 (1238) | 2.76 (1.28) | 2829 (1267) |
| Fed (N = 26)     | 79.1 (26.3)* | 5.3 (2.1)* | 0.000117 (0.00046) | 700 (307) | 4885 (1483)* | 1.78 (0.54)* | 1708 (724)* |

*Significantly different to fasted value, P < 0.015.

SD = standard deviation; C\text{max} = peak plasma concentration; t\text{max} = time to C\text{max}; λ\text{z} = terminal-phase disposition rate constant; t\text{½} = terminal-phase elimination half-life; AUC = area under concentration-time curve; CL/F = apparent oral dose clearance; V\text{z/F} = apparent volume of distribution.
In this study, moxidectin was reported to be generally well tolerated in both the fasted and fed cohorts. Drug-related TEAEs were relatively infrequent, similarly distributed across the fasted and fed cohorts, and were similar to those reported in a previous phase I clinical study. The TEAEs reported during the inpatient and long outpatient phases were generally found to be mild seasonal infections that took place during the outpatient phase. No SAEs were reported during the study and no subject withdrew from the study as a result of AEs. There were no clinically relevant changes in vital signs, safety laboratory tests, and ECGs (no prolongation of the QTc interval) during this study.

This study shows that consumption of food increases the bioavailability of moxidectin compared with drug administration in the fasting state. In addition, moxidectin was found to be generally well tolerated when taken in tablet form, with or without food. Furthermore, the known safety profile of moxidectin in both healthy volunteers and patients suggests that the clinical impact of administration with food in subsequent clinical trials of moxidectin should be minimal. A phase III trial of moxidectin for the treatment of onchocerciasis in humans is ongoing.

Received June 28, 2011. Accepted for publication September 9, 2011.

Acknowledgments: This study was supported by Wyeth Research, which was acquired by Pfizer, Inc. in October 2009. Medicis Medical Science Services conducted the study, and Dr. Fleckenstein of the University of Iowa provided bioanalytical analysis, funded by Wyeth Research, now Pfizer, Inc. Editorial support was provided by Karen Irving at Complete Medical Communications and was funded by Pfizer, Inc.

Disclosure: Some of the authors are employed by Pfizer, Inc., the makers of moxidectin and hold stock in the company. This statement is made in the interest of full disclosure and not because the authors consider this to be a conflict of interest.

Authors’ addresses: Joan M. Korth-Bradley, Ian Gourley, Kyle Matschke, and Karine Cailleux, Pfizer, Inc., Collegeville, PA, E-mails: joan.korth-bradley@pfizer.com, Kyle.Matschke@pfizer.com, Ian.Gourley@pfizer.com, and Karine.Cailleux@pfizer.com. Virginia Parks and Stephen Chalon, Pfizer Global Research and Development, Coeur D’Alene – Tour A – La Defense 4, 92931 Paris La Defense Cedex, France, E-mails: Vparks@shire.com and Stephan.chalon@roche.com. Serge Fitoussi, Medicis Poitiers, Poitiers, France, E-mail: Serge.Fitoussi@mediscis.com. Lawrence Fleckenstein, College of Pharmacy, University of Iowa, Iowa City, IA, E-mail: L-Fleckenstein@uiowa.edu.

REFERENCES

1. APOC, 2005. Final communique: eleventh session of the Joint Action Forum. Available at: http://www.who.int/apoc/about/structure/jaf/en/index.html. Accessed November 2, 2010.
2. World Health Organization, 2010. Working to overcome the global impact of neglected tropical diseases: first WHO report on neglected tropical diseases. Available at: http://www.who.int/neglected_diseases/2010report/en/. Accessed November 8, 2010.
3. Basáñez MG, Boussinesq M, 1999. Population biology of human onchocerciasis. Philos Trans R Soc Lond B Biol Sci 354:809–826.
4. Plaisier AP, van Oortmerssen GJ, Remme J, Habbema JD, 1991. The reproductive lifespan of Onchocerca volvulus in West African savanna. Acta Trop 48:271–284.
5. Cotreau MM, Warren S, Ryan JL, Fleckenstein L, Vanapalli SR, Brown KR, Rock D, Chen C-Y, Schwertschlag US, 2003. The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. J Clin Pharmacol 43:1108–1115.
6. Forrestar SG, Prichard RK, Beech RN, 2002. A glutamate-gated chloride channel subunit from Haemonchus contortus: expression in a mammalian cell line, ligand binding, and modulation of anthelmintic binding by glutamate. Biochem Pharmacol 63:1061–1068.
7. Cully DF, Vassilatis DK, Liu KK, Pares P, Van der Ploeg LH, Schaeffer JM, Arena JP, 1994. Cloning of an avermectin-sensitive glutamate-gated chloride channel from Caenorhabditis elegans. Nature 371:707–711.
8. Zulalian J, Stout SJ, daCunha AR, Garces T, Miller P, 1994. Absorption, tissue distribution, metabolism, and excretion of moxidectin in cattle. J Agric Food Chem 42:381–387.
9. Parks V, Patat A, Mayer P, Fleckenstein L, Weber W, 2004. Relative bioavailability of liquid and tablet formulations of the antiparasitic moxidectin. Clin Exp Pharmacol Physiol 31:128.
10. Wu C-Y, Benet LZ, 2005. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res 22:11–23.
11. Gershkovich P, Hoffman A, 2007. Effect of a high-fat meal on absorption and disposition of lipophilic compounds: the importance of degree of association with triglyceride-rich lipoproteins. Eur J Pharm Sci 32:24–32.
12. Chen YC, Hung YP, Fleckenstein L, 2002. Liquid chromatographic assay of moxidectin in human plasma for application to pharmacokinetic studies. J Pharm Biomed Anal 29:917–926.