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CLINICAL THERAPEUTICS

Randomized Trial of Food Effect on Pharmacokinetic Parameters of ABX464 Administered Orally to Healthy Male Subjects

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ABSTRACT ABX464 is an antiviral that provides a novel approach to the reduction and control of HIV infection. Investigation of food influence is important in the optimization of treatment. An open-label, food effect, randomized study which included 2 groups of 24 subjects each was carried out to assess the bioavailability and safety of single (group 1) and repeated (group 2) oral doses of ABX464 (50 mg) under fed or fasted conditions. The maximum concentration (C_{max}) and the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) of ABX464 were demonstrated to increase with food after a single dose of ABX464 (219% and 188%, respectively). The apparent terminal elimination half-lives ($t_{1/2}$s) under fed and fasted conditions were comparable, at about 0.80 h. The median time to maximum concentration (T_{max}) was delayed from 1.5 to 2.8 h, and the ratio of the $AUC_{0-\infty}$ obtained under fed conditions to the $AUC_{0-\infty}$ obtained under fasted conditions (F_{rel}) was 2.69. Comparable results were obtained on day 1 and day 10 in group 2. The increases in C_{max} and $AUC_{0-\infty}$ of the metabolite ABX464–N-glucuronide (ABX464-NGlc) were, however, much more limited when ABX464 was given with food. The $t_{1/2}$s were also comparable under the two conditions (around 100 h). Between day 1 and day 10, the C_{max} increased by 5% under the fasted condition and by 25% under the fed condition. The most common related treatment-emergent adverse events were headaches, vomiting, and nausea. It was concluded that food has a significant impact on the levels of ABX464 in plasma with a delay in absorption and increased relative bioavailability, with a lesser impact on its biotransformation into ABX464-NGlc. ABX464 was well tolerated under both fasted and fed conditions. (This study has been registered at ClinicalTrials.gov under registration no. NCT02731885.)

KEYWORDS ABX464, HIV, food effect, pharmacokinetics, safety, human immunodeficiency virus

Received 17 June 2016 **Returned for modification** 10 August 2016 **Accepted** 23 October 2016

Accepted manuscript posted online 31 October 2016

Citation Scherrer D, Rouzier R, Cardona M, Barrett PN, Steens J-M, Gineste P, Murphy RL, Tazi J, Ehrlich HJ. 2017. Randomized trial of food effect on pharmacokinetic parameters of ABX464 administered orally to healthy male subjects. Antimicrob Agents Chemother 61:e01288-16. https://doi.org/10.1128/AAC.01288-16.

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More than 30 million people are still infected with human immunodeficiency virus (HIV) (1). Access to highly active antiretroviral therapy (HAART), based upon the combination of HIV protease and reverse transcriptase inhibitors, has dramatically changed the prognosis of HIV infection (2, 3). As a result, HIV is now considered a chronic disease in many countries (4). However, long-term use of HAART is limited by issues of drug resistance and side effects, even with new classes of anti-HIV/AIDS drugs (5–8). Another issue is the occurrence of viral rebound when therapy is terminated (9). There is a continuing need for new drugs, in particular for those acting through novel mechanisms of action to achieve HIV infection cure (10).

There are a number of different classes of drugs that are currently licensed to treat HIV infection. None of these drugs can eliminate virus reservoirs, and all are subject to the development of drug-resistant variants. ABX464 is a first-in-class small molecule that modulates viral RNA splicing events (11). RNA splicing is an essential step required for the production of viral infectious particles. A balanced production of spliced and unspliced viral RNA is essential for virus replication (12, 13). This unique feature of the HIV replication cycle, which requires both activation and inhibition of splicing of viral precursor mRNAs, has been utilized to generate a compound with a unique mechanism of viral replication inhibition. This inhibition is achieved by modulating the splicing of viral RNA and thereby interfering with the production of the essential regulatory proteins Rev and Tat or by inhibiting the export of viral mRNA required for Gag, Pol, and Env production and for generation of genomic RNA. ABX464 inhibits the export of unspliced viral RNA mediated by Rev, which is an essential step for virus replication, and due to this specificity does not impact normal cellular splicing (11, 14, 15).

ABX464 has been demonstrated to be effective in inhibiting the replication of different HIV subtypes in peripheral blood mononuclear cells (PBMCs) and macrophages and did not induce any drug resistance for up to 24 weeks of treatment *in vitro* (11). ABX464 also substantially reduced virus replication in two humanized models of mice infected with HIV-1, and this was followed by a long-lasting effect on the viral load after treatment termination (11). ABX464 represents the first HIV therapy able to reduce the expression of the HIV-1 proviral genome and to maintain a low viral load after treatment termination. Therefore, ABX464 is a strong clinical candidate providing a unique approach to the reduction and control of HIV infection.

A first-in-man (FIM) study has been completed to determine pharmacokinetic (PK) and safety profiles of ABX464. This study confirmed that ABX464 is well tolerated and rapidly and substantially metabolized into ABX464–N-glucuronide (ABX464-NGlc) in human subjects (16). Preclinical studies have also demonstrated that the ABX464-NGlc metabolite has antiviral properties in HIV-infected macrophages *in vitro*, which may play a role in the long-lasting antiviral effect of ABX464 after treatment termination in mouse model (11). For this reason, the PK properties of the metabolite may also be of particular therapeutic importance.

Food influence can be very important in the absorption of medicines, because food can lead to inefficiency in treatment or an increase in adverse events (AEs). It is important to investigate the food effect on the plasma levels of the drug in order to accordingly adapt doses for patients and optimize the treatment. This study was initiated to determine the effects of food on the pharmacokinetic (PK) parameters of ABX464 and its metabolite ABX464-NGlc after a single dose or multiple oral doses of 50 mg of ABX464.

RESULTS

Baseline characteristics and patient disposition. Twenty-four male subjects aged from 20 to 53 years (mean, ~35 years) and with a body mass index (BMI) of 17.4 to 28.2 kg/m^2 were included in group 1, and 24 male subjects aged from 18 to 53 years (mean, ~34 years) and with a BMI of 17.9 to 28.0 kg/m^2 were included in group 2. In group 2, the BMIs were similar in each food condition subgroup (23.89 $\pm$ 3.69 kg/m^2 and 24.37 $\pm$ 2.82 kg/m^2 in fasted and fed conditions, respectively) (data not shown).

At screening, no clinically significant abnormalities were detected in the medical history, physical examination, laboratory test, urinalysis, vital signs, and electrocardiogram (ECG) parameters. All of the included subjects received the treatment as planned in the protocol and were analyzed in the safety analysis. Regarding the PK analysis set, 6 subjects (5 in group 1 and 1 in group 2) experienced vomiting episodes on day 1 more than 2 h after administration. This was considered to have no impact on PK parameters, and thus all the subjects/periods were kept in the PK population except a subject in group 1 with no quantifiable ABX464 plasma concentrations after administration of ABX464 without food (treatment A). This subject also had an ABX464-NGlc profile totally inconsistent with other subjects, with measured plasma concentrations

TABLE 1 Summary of descriptive statistics of ABX464 PK parameters after a single oral administration of 50 mg ABX464 under fasted and fed conditions to group 1 subjects[a]

Condition and/or value	C_{max} (ng/ml)	T_{max}[b] (h)	AUC_{0-t} (ng · h/ml)	$AUC_{0-\infty}$ (ng · h/ml)	$t_{1/2}$ (h)	F_{rel}
Fasted	$n = 23$	$n = 23$	$n = 23$	$n = 17$	$n = 17$	
Mean	17.70	1.5	42.78	51.74	0.88	
SD	13.53	1.0–6.0	28.57	29.66	0.28	
GM	13.70		34.52	43.93	0.83	
Fed	$n = 24$	$n = 24$	$n = 24$	$n = 13$	$n = 13$	$n = 10$
Mean	50.21	2.8	121.73	135.51	0.87	3.67
SD	22.97	1.2–4.0	51.25	50.55	0.40	2.62
GM	43.71		109.27	126.34	0.79	2.69
Point estimate	3.16		3.12	NC		
90% CI	2.45–4.07		2.55–3.82	NC		

[a]C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$, AUC from time zero to infinity; $t_{1/2}$, apparent terminal elimination half-life; F_{rel}, ratio of $AUC_{0-\infty}$ obtained in fed conditions to $AUC_{0-\infty}$ obtained in fasted conditions; *n*, number of subjects; SD, standard deviation; GM, geometric mean; NC, not calculated; CI, confidence interval.

[b]Instead of means and standard deviations, the values given for this parameter are medians and ranges (minimum–maximum), respectively.

ranging between approximately 2.5 and 4 ng/ml from predose to 48 h postdose. There was a strong suspicion that this patient did not actually swallow his treatment despite a mouth examination.

PK. (i) Group 1. The pharmacokinetic profiles of ABX464 after a single 50-mg oral administration under fasted and fed conditions are described in Table 1. The first quantifiable ABX464 plasma concentration was observed at 0.5 h postdose in most subjects, under both fasted and fed conditions. Plasma levels of ABX464 were increased when the drug was given concomitantly with food. Geometric mean (GM) values of maximum concentration (C_{max}), area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), and AUC from time zero to the time of last quantifiable concentration (AUC_{0-t}) were 43.71 ng/ml, 126.34 ng · h/ml, and 109.27 ng · h/ml under fed conditions, compared to 13.7 ng/ml, 43.93 ng · h/ml, and 34.52 ng · h/ml, respectively, under fasted conditions, i.e., 219%, 188%, and 217% higher than under fasted conditions. GM apparent terminal elimination half-lives ($t_{1/2}$s) were comparable in terms of mean values and variability (0.83 and 0.79 h under fasted and fed conditions with coefficients of variation [CV] of 32% and 46%, respectively). The median time to maximum concentration (T_{max}) was delayed from 1.5 to 2.8 h, suggesting a prolongation of the absorption phase. Interindividual variability tended to decrease when ABX464 was given with food, since the CVs of AUC_{0-t} and $AUC_{0-\infty}$ under fasted conditions were 67% and 57% compared to 42% and 37%, respectively, under fed conditions. The ratio of the $AUC_{0-\infty}$ obtained under fed conditions to the $AUC_{0-\infty}$ obtained under fasted conditions (F_{rel}), based on GM values of estimated $AUC_{0-\infty}$, was 2.69, with an interindividual variability of 71%. Formal statistical analysis fully confirmed these observations, since the lower limits of the 90% confidence interval (CI) of C_{max} and AUC_{0-t} were 2.45 and 2.55 with point estimates of 3.16 and 3.12, respectively. Formal statistical analysis was not run on the $AUC_{0-\infty}$ (missing data). With treatment A (single treatment under fasted conditions), the terminal plasma elimination rate constant (k_{el}) could be properly determined in only 17 subjects. It could not be determined or validated in seven cases for different reasons. In one subject, only two data points were available in the elimination phase. For five subjects, no linear regression or very poor regression could be drawn in the elimination phase and one subject had no detectable ABX464 under fasted conditions. With treatment B (single treatment under fed conditions), the k_{el} could be properly determined in only 13 subjects. It could not be determined or validated in 11 cases for the following reasons. For eight subjects, only two points were available in the elimination phase. No linear regression or very

TABLE 2 Summary of descriptive statistics of ABX464-NGlc PK parameters after a single oral administration of 50 mg ABX464 under fasted and fed conditions to group 1 subjects[a]

Condition and/or value	C_{max} (ng/ml)	T_{max}[b] (h)	AUC_{0-t} (ng · h/ml)	$AUC_{0-\infty}$ (ng · h/ml)	$t_{1/2}$ (h)
Fasted	$n = 23$	$n = 24$	$n = 23$	$n = 23$	$n = 23$
Mean	2,938.13	4.0	203,520.82	204,111.81	99.36
SD	1,449.61	3.0–8.0	103,601.77	103,565.29	19.02
GM	2,572.81		181,212.30	181,923.37	97.58
Fed	$n = 24$	$n = 24$	$n = 24$	$n = 24$	$n = 24$
Mean	2,751.54	4.0	194,660.83	195,497.81	100.76
SD	1,377.29	2.8–6.0	95,768.93	95,783.65	22.40
GM	2,401.52		170,773.84	171,712.64	98.37
Point estimate	0.93		0.93	0.93	
90% CI	0.74–1.16		0.77–1.14	0.77–1.14	

[a] C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$, AUC from time zero to infinity; $t_{1/2}$, apparent terminal elimination half-life; *n*, number of subjects; SD, standard deviation; GM, geometric mean; CI, confidence interval.

[b] Instead of means and standard deviations, the values given for this parameter are medians and ranges (minimum–maximum), respectively.

bad fitting of the elimination phase could be drawn in the elimination phase for another three subjects. Therefore, for all these cases, k_{el} as well as PK parameters derived from k_{el} are not presented.

ABX464 was substantially metabolized into ABX464-NGlc after a single oral administration of 50 mg under fed or fasted conditions. Due to the demonstrated antiviral activity of ABX464-NGlc (11), the PK characteristics of this metabolite may be of particular therapeutic importance. Descriptive statistics of derived ABX464-NGlc PK parameters are summarized in Table 2 for 23 of 24 subjects. One subject presented a very atypical ABX464-NGlc PK profile, suggesting a lack of treatment compliance (subject did not swallow the treatment), which could not formally be confirmed. Therefore, it was decided to exclude this subject's derived PK parameters directly related to plasma concentrations to avoid a bias in the determination of descriptive statistics of the group.

The data presented in Table 2 demonstrate are substantially different for all ABX464-NGlc PK parameters from those for the parent ABX464 compound, under both fasted and fed conditions. The GM values for C_{max} and $t_{1/2}$ were approximately 190- and 120-fold higher, respectively, than those for the parent compound under fasted conditions. However, the pattern with respect to PK parameter differences under fasted and fed conditions was different from that seen for the parent compound. The GM value of the C_{max} of ABX464-NGlc given under fed conditions (2,401.52 ng/ml) was 7% lower than that when ABX464 was given under fasted conditions (2,572.81 ng/ml), while the GM $AUC_{0-\infty}$ was 6% lower. The interindividual variability of both parameters obtained under fasted and fed conditions were roughly comparable at about 50%. The GM $t_{1/2}$s were also comparable under both conditions and corresponded to what was previously reported (i.e., around 100 h). Formal statistical analysis supported the limited variation previously described, since point estimates of C_{max} and $AUC_{0-\infty}$ were 0.93 and the limits of the corresponding 90% CI were almost within the bioequivalence limits (0.8000 to 1.2500).

(ii) Group 2. In group 2, 50 mg ABX464 was orally administered on days 1, 4, 7, and 10 either after overnight fasting or after a high-fat breakfast. Descriptive statistics of derived PK parameters of ABX464 under fasted and fed conditions on day 1 and day 10 are summarized in Table 3. Plasma levels of ABX464 were substantially increased when the drug was given concomitantly with food. Day 1 GM values for C_{max} and AUC_{0-t} were 42.92 ng/ml and 105.22 ng · h/ml under fed conditions compared to 10 ng/ml and 26.92 ng · h/ml, respectively, under fasted conditions, i.e., 329% and 291% higher. GM

TABLE 3 Summary of descriptive statistics of ABX464 PK parameters after the first and fourth single oral administration of 50 mg ABX464 (day 1 and day 10) under fasted and fed conditions to group 2 subjects[a]

Condition and/or value	Day 1				Day 10			
	C_{max} (ng/ml)	T_{max}[b] (h)	AUC_{0-t} (ng · h/ml)	$t_{1/2}$ (h)	C_{max} (ng/ml)	T_{max}[b] (h)	AUC_{0-t} (ng · h/ml)	$t_{1/2}$ (h)
Fasted	$n = 12$	$n = 12$	$n = 12$	$n = 4$	$n = 12$	$n = 12$	$n = 12$	$n = 9$
Mean	11.19	1.75	31.49	1.11	10.75	1.8	28.26	1.15
SD	4.98	1.00–2.50	18.28	0.68	4.63	1.0–3.0	14.82	0.52
GM	10.00		26.92	0.99	9.93		25.16	1.08
Fed	$n = 12$	$n = 12$	$n = 12$	$n = 6$	$n = 12$	$n = 12$	$n = 12$	$n = 8$
Mean	46.67	2.50	112.66	0.77	55.38	2.3	111.24	0.74
SD	16.45	2.00–4.00	39.52	0.14	43.04	1.5–4.0	72.43	0.15
GM	42.92		105.22	0.76	42.79		93.19	0.73
Point estimate	4.29		3.91		4.31		3.70	
90% CI	3.03–6.08		2.74–5.58		2.82–6.59		2.51–5.47	

[a]C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$, AUC from time zero to infinity; $t_{1/2}$, apparent terminal elimination half-life; *n*, number of subjects; SD, standard deviation; GM, geometric mean; CI, confidence interval.

[b]Instead of means and standard deviations, the values given for this parameter are medians and ranges (minimum–maximum), respectively.

$t_{1/2}$s were roughly comparable (0.99 and 0.76 h under fasted and fed conditions), but interindividual variability, as expressed by the ratio of the standard deviation to the mean value, was reduced under fed conditions (19% under fed conditions versus 61% under fasted conditions). The median T_{max} was delayed from 1.75 to 2.5 h. These results were consistent with those reported in group 1. Results obtained on day 10 were very comparable to those obtained on day 1. With concomitant food intake, GM values of C_{max} and AUC_{0-t} were also substantially higher (415% and 294% higher, respectively). GM $t_{1/2}$s were roughly comparable (1.08 and 0.73 h under fasted and fed conditions), and interindividual variability remained lower under fed conditions (20% versus 46%). However, it should be noted that reliable $t_{1/2}$s could be determined on days 1 and 10, respectively, only in 4 and 9 subjects in the fasted state and 6 and 8 subjects in the fed state. For the other subjects, elimination could not be delineated properly (poor r^2 value, insufficient data in the elimination phase, too large a percentage of extrapolated AUC).

The results of formal statistical analysis were also consistent with the day 1 point estimates for both C_{max} and AUC_{0-t} of 4.29 and 3.91, respectively, confirming the substantial impact of concomitant food intake on plasma levels of ABX464. Results obtained on day 10 were comparable.

Descriptive statistics of derived PK parameters of ABX464-NGlc after the first and fourth oral administration of 50 mg ABX464 under fasted and fed conditions are summarized in Tables 4 and 5, respectively. In all cases, no reliable evaluation of the terminal phase could be done on day 1 as a result of the high residual value measured prior to the receipt of the next dose. The k_{el} determination on day 10 was, however, always very robust, with a negligible percentage of extrapolated AUC.

After the first administration of ABX464, the PK parameter values were substantially different for ABX464-NGlc compared to those measured for the parent drug, under both fasted and fed conditions; e.g., the GM values of the C_{max} for the metabolite were approximately 200-fold higher than those measured for the parent compound under fasted conditions. In addition, smaller differences between PK parameters under fasted and fed conditions for ABX464-NGlc were again observed. The GM value of the C_{max} of ABX464-NGlc was only 14% higher when ABX464 was given with food, while the GM AUC_{0-t} was 11% higher (Table 4). The interindividual variabilities of the two parameters obtained under fasted and fed conditions were roughly comparable at about 40%, and point estimates for the two parameters were about 1.1. After the fourth administration, differences in ABX464-NGlc PK parameters under fasted and fed conditions were somewhat larger than those after the first, with GM values for the C_{max} and AUC_{0-t}

TABLE 4 Summary of descriptive statistics of NGlcABX464 PK parameters after the first oral administration of 50 mg ABX464 under fasted and fed conditions (day 1) to group 2 subjects[a]

Condition and/or value	C_{max} (ng/ml)	T_{max}[b] (h)	AUC_{0-t} (ng · h/ml)
Fasted	$n = 12$	$n = 12$	$n = 12$
Mean	2,126.67	4.00	52,858.43
SD	833.06	3.00–6.00	19,379.54
GM	1,993.60		49,915.49
Fed	$n = 12$	$n = 12$	$n = 12$
Mean	2,475.08	4.00	60,092.14
SD	1,002.79	4.00–6.03	24,108.49
GM	2,269.31		55,426.28
Point estimate	1.14		1.11
90% CI	0.85–1.52		0.84–1.46

[a]C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of last quantifiable concentration; *n*, number of subjects; SD, standard deviation; GM, geometric mean; CI, confidence interval.
[b]Instead of means and standard deviations, the values given for this parameter are medians and ranges (minimum–maximum), respectively.

being 35% and 33% higher, respectively, when ABX464 was given with food (Table 5). Formal statistical analysis confirmed that the increases in C_{max} and AUC of ABX464-NGlc were much more limited than those of the parent drug.

Between day 1 and day 10, the GM C_{max} increased by 5% under fasted conditions and by 25% under fed conditions. GM values of $t_{1/2}$ on day 10 were similar under the two conditions and were comparable to those previously reported for group 1.

Safety and tolerability. A total of 50 treatment-emergent AEs (TEAEs) (27 under fasted conditions and 23 under fed conditions) were reported by 21 subjects out of 48 (data not shown). All of them were of mild to moderate intensity except for 1 case of severe abdominal injury not related to ABX464. The most frequent TEAEs consisted of headaches (29% of the subjects), nausea (12.5% of the subjects), and vomiting (12.5% of the subjects). Headache generally appeared in the very first hours after investigational medicinal product (IMP) administration. The frequency tended to decrease with the number of administrations in group 2. Episodes of vomiting occurred mainly in group 1 (5 out of 6 subjects). In two subjects, vomiting was reported just after nausea. Concomitant food intake did not appear to reduce this side effect, as 4 subjects vomited under fed conditions and 2 under fasting conditions. There was 1 serious AE

TABLE 5 Summary of descriptive statistics of ABX464-NGlc PK parameters after the fourth oral administration of 50 mg ABX464 under fed and fasted conditions (day 10) in group 2 subjects[a]

Condition and/or value	C_{max} (ng/ml)	T_{max}[b] (h)	AUC_{0-t} (ng · h/ml)	$AUC_{0-\infty}$ (ng · h/ml)	$t_{1/2}$ (h)
Fasted	$n = 12$	$n = 12$	$n = 12$	$n = 12$	$n = 12$
Mean	2,314.25	4.00	244,319.92	245,171.27	101.72
SD	1,011.19	3.00–6.00	139,006.91	139,224.18	29.11
GM	2,099.95		206,875.99	207,700.73	98.08
Fed	$n = 12$	$n = 12$	$n = 12$	$n = 12$	$n = 12$
Mean	3,245.00	4.00	325,474.37	326,237.38	101.39
SD	2,128.91	2.62–8.00	241,001.77	241,212.80	20.85
GM	2,845.01		276,156.04	276,923.59	99.47
Point estimate	1.35		1.33	1.33	
90% CI	0.96–1.91		0.88–2.03	0.88–2.02	

[a]C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$, AUC from time zero to infinity; $t_{1/2}$, apparent terminal elimination half-life; *n*, number of subjects; SD, standard deviation; GM, geometric mean; CI, confidence interval.
[b]Instead of means and standard deviations, the values given for this parameter are medians and ranges (minimum–maximum), respectively.

(SAE) in each group resulting from an accident and an intercurrent disease (acute gastroenteritis 26 days after the last dosing). None of these could be reasonably related to ABX464. No AEs led to premature discontinuation.

No changes or clinically significant abnormalities in either laboratory parameters, vital signs, or ECG parameters were observed.

DISCUSSION

A FIM study to determine the safety profile as well as the PK parameters of ABX464 has previously been reported (16). This study was carried out with a single dose of 50, 100, 150, or 200 mg after overnight fasting, and the product was reported to be safe and well tolerated at all doses. Food-drug interaction can, however, cause increases, decreases, or delays in the bioavailability of an orally delivered antiviral agent; foods may have no effect on the absorption of the drug, or they may improve the gastrointestinal tolerance. The interactions between the different classes of licensed HIV antivirals and food may vary widely, and recommendations for use vary from take with food, take without food, or take with or without food.

The impact of concomitant food intake on the C_{max} and AUC of ABX464 and of its main metabolite was investigated in this study after a single oral administration of 50 mg ABX464 (group 1) and after 4 consecutive administrations of 50 mg ABX464 over 10 days (group 2). Repeated-dose administration was investigated for the first time with this study, and a dosing interval of 3 days was chosen as a conservative schedule for safety reasons. Also, as this study was the first to investigate food effect and repeated dosing, it does have a number of intrinsic limitations. At this early stage in the clinical development program, before safety had been established in human trials under the conditions described above, it was not considered appropriate to include HIV-infected subjects in the study, although it is recognized that HIV infection can alter the gut flora and patterns of gut metabolism. In addition, in order to eliminate any potential risk in the event of contraceptive failure, female subjects were not included in this study. The study is further limited in that no age effects could be analyzed, as the study was done with low subject numbers ($n = 24$ in each group), in the 18- to 55-year age group, as is standard for such early studies. Future studies are being designed to include females, HIV-infected subjects, and other age groups. In addition, the results of the study demonstrated that blood sampling done more frequently from days 2 through 10 in the single-dose group might have provided a more accurate $t_{1/2}$ determination in the that group.

The results of the study reported here demonstrated that PK parameters under fasted conditions were consistent with those observed in the FIM study (16). Food intake was found to markedly increase plasma levels of ABX464. In group 1, the C_{max} and $AUC_{0-\infty}$ of ABX464 were about 3-fold higher and the T_{max} was approximately doubled in the presence of food. Formal statistical analysis confirmed the significance of the increase observed for ABX464 (Table 1). In group 2, results obtained after the first drug administration were in line with results in group 1 and no marked changes were observed on day 10 (Table 3).

The PK parameters of the metabolite ABX-464NGlc under fasted conditions in group 1 were also fully consistent with the data previously reported from the FIM study. The GM of the C_{max} for ABX464-NGlc was approximately 190-fold higher than that for the parent compound under fasted conditions in group 1, and the $t_{1/2}$ was approximately 100-fold longer (Tables 1 and 2). However, in contrast to the situation seen with the parent compound, the increases in the C_{max} and AUCs of ABX464-NGlc were much more limited than those seen for the parent compound. In fact, in group 1, the GMs of C_{max} and $AUC_{0-\infty}$ were slightly decreased (less than 10%) under fed conditions. In group 2, a slightly enhanced plasma availability was observed, with increased C_{max} values of 14% and 35% being observed after the first and fourth administrations, respectively, under fed compared to fasted conditions (Tables 4 and 5).

In total, these results demonstrate a substantial positive effect of food on the

administration of ABX464, with a delay in absorption and an increased bioavailability. A much more limited impact of food was seen on the metabolite ABX464-NGlc. Also, as had previously been reported, the metabolite exhibited markedly higher blood concentrations than the parent compound, with close to a 200-fold higher C_{max}, and had a much higher (approximately 100-fold) $t_{1/2}$. These results may be of therapeutic significance in that it has been reported that ABX464-NGlc is as efficient as the parent compound in inhibiting HIV-1 replication in primary macrophages *in vitro* (11) and the prolonged bioavailability may contribute to prolonging and amplifying ABX464 antiviral activity. This antiviral activity of ABX464-NGlc has been seen only in macrophages, not T cells. Thus, the enhanced bioavailability of the parent compound ABX464 under fed conditions might also favor enhanced antiviral effects of the compound under these administration conditions. However, as it is likely that ABX464 would be used in combination with other classes of anti-HIV drugs, additional food effect studies will be required with such combinations to investigate the impact of food on PK parameters.

With respect to the safety and tolerability of ABX464, the most common ABX464-related TEAEs were headaches and gastrointestinal disorders (vomiting and nausea). These results were consistent with those of previous preclinical and clinical (16) studies. A review of the rate of headaches suggested that this effect could be a first-dose effect, tending to disappear in the case of chronic treatment. Vomiting episodes were not reduced with concomitant food intake (4 subjects experienced vomiting in the fed group compared to 2 in the fasted group). However, it could be concluded that the product was safe and well tolerated under both conditions of administration and according to both drug regimens tested.

Together with the previous study reporting on FIM use of the product, these are the first studies describing the safety, tolerability, bioavailability, and metabolism of ABX464. The data obtained from these studies warrant further investigation of this compound in HIV-infected subjects. A phase IIa dose escalation study with different dose schedules is currently ongoing. This study was designed to investigate safety, PK, and viral kinetic effects of ABX464 in previously untreated patients with HIV infection and will provide the first data on the anti-HIV effects of ABX464 in humans with different doses and schedules.

MATERIALS AND METHODS

Study population. Forty-eight healthy male subjects in good health on the basis of medical history, physical examination, vital signs, electrocardiogram (ECG), and routine laboratory safety tests, aged from 18 to 55 years, with BMIs of 17 to 28 kg/m^2, and who were nonsmokers or light smokers ($\leq$5 cigarettes per day) without history of frequent headache and/or migraine, recurrent nausea, and/or vomiting were included after having given their written informed consent.

The study (protocol no. ABX464-FE-001) was approved by the Clinical Research Regulatory Council in Mauritius and conducted between October 2014 and June 2015 in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Study design. This phase I study consisted of an open-label, food-effect, randomized study divided into 2 groups and performed at a single site (CAP Research, Phoenix, Mauritius). Twenty-four subjects were enrolled in each group in order to have 20 evaluable subjects per group (data not shown). In the first group, a crossover design, 24 subjects received a single dose of 50 mg of ABX464 on 2 occasions (once under fasted conditions [treatment A] and once under fed conditions [treatment B]), separated by a washout period of at least 45 days. In the second group, a parallel design, 24 subjects received 50 mg of ABX464 every 3 days during 10 days under the fasted (treatment A) or fed (treatment B) condition. Two groups were included, as this was the first repeated-dose study, and a fixed dose (50 mg) was selected in order to ensure a reliable comparison between groups 1 and 2, i.e., after single and repeated administrations, respectively. The second group involved the repeated-dose investigation with a conservative interval of 3-day dosing being chosen primarily because of safety considerations and also to assess whether this regimen was sufficient to maintain the metabolite at high levels. A crossover design was utilized in the single-dose group in order to enable reliable comparisons between groups, but a parallel design was selected for the multiple-dose group in order to enable repeated administrations in a shorter period of time. According to the study group, the subjects were randomly allocated, using a predefined randomization list (PLAN Procedure using SAS software version 9.3), to a treatment sequence or a treatment in the chronological order of their entry into the study.

A screening visit was performed within 3 weeks prior to treatment, including physical examination, medical history, serology (hepatitis C virus [HCV], hepatitis B virus [HBV], and HIV), urine drug screen,

alcohol breath test, laboratory test, urinalysis, vital signs, and ECG. Subjects were hospitalized from the day prior to dosing until the morning of day 2 on two occasions in group 1 and from the day prior to dosing until the morning of day 11 in group 2. The consumption of alcoholic beverages, caffeine- or xanthine-containing products, and grapefruit or grapefruit juice was prohibited from 48 h prior to dosing until 48 h posttreatment.

In group 1, a single oral dose of ABX464 (50 mg; two 25-mg capsules) was administered on the morning of day 0 of each period either after overnight fasting or after a high-fat breakfast. Follow-up visits were planned on days 3, 10, 17, 24, 31, 38, and 45 of each period for PK samples and AEs. Safety assessments consisted of physical examination, laboratory tests, urinalysis, vital signs, and ECG performed on day 1 of each period and on day 3 of period 2.

In group 2, ABX464 (50 mg) was administered on days 1, 4, 7, and 10 either after overnight fasting or after a high-fat breakfast. Follow-up visits were planned on days 12, 17, 24, 31, 38, 45, 52, and 59 for PK samples and AEs. Safety assessments consisted of physical examination, laboratory tests, urinalysis, vital signs, and ECG performed on day 1 and day 11. All treatment-emergent adverse events (defined as any event not present prior to the initiation of treatment or any event already present that worsened in either intensity or frequency following exposure to treatment) were reported.

Endpoints. The objectives of this study were to assess the relative bioavailability of single and repeated oral doses of 50 mg of ABX464 under fed or fasted conditions and to assess the clinical and biological tolerability of ABX464.

Pharmacokinetic analysis. For assessment of ABX464 and ABX464-NGlc plasma levels, blood samples were collected in group 1 before administration, at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 h postdose, and at follow-up visits (days 10, 17, 24, 31, 38, and 45) of each period. In group 2, blood samples were collected on day 1 and day 10 at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 h postdose, on day 4 and day 7 at 0, 2, 4, and 12 h postdose, and then at follow-up visits (days 17, 24, 31, 38, 45, 52, and 59).

Plasma samples were analyzed for ABX464 and ABX464-NGlc by use of validated bioanalytical methods by Atlanbio according to good laboratory practice guidelines.

PK parameters were calculated by noncompartmental analysis. PK parameters calculated on day 1 and day 10 (only for group 2) were the following: maximum concentration (C_{max}), time to maximum concentration (T_{max}), time immediately prior to the first quantifiable plasma concentration (t_{lag}), area under the concentration-time curve from time zero to the time of last quantifiable concentration (AUC_{0-t}) using a linear trapezoidal method, terminal plasma elimination rate constant (k_{el}), AUC from time zero to infinity ($AUC_{0-\infty} = AUC0\text{–}t + C_t/k_{el}$, where C_t is the measured concentration at the time of the last quantifiable concentration), apparent terminal elimination half-life ($t_{1/2} = \ln 2/k_{el}$), ratio of the $AUC_{0-\infty}$ obtained under fed conditions to the $AUC_{0-\infty}$ obtained under fasted conditions (F_{rel}), and for ABX464 only on day 1, apparent total clearance ($CL/F = dose/AUC_{0-\infty}$) and apparent volume of distribution ($V/F = CL/F/k_{el}$).

Statistical analysis. Descriptive statistics were performed on demographic data, vital signs (blood pressure and pulse rate), clinical laboratory parameters, ECG parameters (QT interval, corrected QT interval according to Bazett's formula [QTcB], PR interval, QRS complex, and ventricular rate) and AEs.

Descriptive statistics of PK parameters were performed with Phoenix WinNonlin. Statistical analysis was performed using SAS software version 9.3. Table results and listings were computed with AdClin (version TPF; Build 363 version 3.1 and Build 350 RB version 3.3.1).

In group 1, analysis of C_{max} and AUC was carried out by analysis of variance (ANOVA) using PROC MIXED on the logarithmically transformed data. The analysis of T_{max} was based on descriptive statistics. In group 2, the relative bioavailability was evaluated for PK parameters of day 10 and the comparisons were performed for C_{max}, $AUC_{0-\infty}$, and AUC0–t using a one-way ANOVA model with treatment as the main effect on logarithmically transformed data.

In 2 groups, for each parameter, a point estimate for the ratio of geometric means (GMs) (treatment B to treatment A) was obtained by calculating the difference of least-square means on the logarithmic scale and subsequent back-transformation with the exponential function. Likewise, 90% confidence intervals (CIs) for the ratios were obtained by back-transforming the 90% CIs of least-square mean differences on log-transformed PK parameters.

ACKNOWLEDGMENTS

The study design was provided by D.S., J.T., M.C., J.-M.S., H.J.E., and R.L.M. The study was conducted at CAP Research under the supervision of R.R. Study analyses and manuscript writing were done by P.N.B., P.G., D.S., and J.T.

This work was funded by Abivax, a publicly listed company (formerly known as Splicos).

D.S., J.-M.S., P.G., and H.J.E. are Abivax employees and hold Abivax stock options. P.N.B. and R.L.M. perform consultancy services for Abivax. R.R. was the principal investigator of the study, and M.C. was the study coordinator at site; they received consultancy fees. J.T. is member of a collaborative laboratory that has received financial support from Abivax.

We acknowledge all the volunteers who participated in this study for their continued availability and commitment to the study.

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