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Pharmacokinetics and tolerability of ABX464, a novel first-in-class compound to treat HIV infection, in healthy HIV-uninfected subjects

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Background: An anti-HIV compound (ABX464) has been developed with a novel mechanism of activity in that it blocks viral gene expression in cells that are already infected.

Objectives: A first-in-man study was conducted to determine the pharmacokinetic and safety profiles of ABX464. This was carried out as an open label, parallel group, single ascending dose, exploratory study.

Methods: Twenty-four male subjects in good health without HIV infection, aged from 18 to 55 years old, with BMIs of 18–27 kg/m^2 were included. A single oral dose of ABX464 (50, 100, 150 or 200 mg) was administered on the morning of day 0 after overnight fasting, with follow-up for 45 days. Safety assessments consisted of vital signs, electrocardiogram, physical examination, laboratory tests and urinalysis. Pharmacokinetic parameters were calculated for ABX464 and its main metabolite ABX-464-*N*-glucuronide (ABX464-NGlc). The study was registered at https://www.clinicaltrials (trial number NCT02792686).

Results: ABX464 was well tolerated; the most frequent related treatment-emergent adverse events were headaches, nausea and vomiting; they were not considered as treatment-limiting effects. ABX464's C_{max} was observed approximately 2 h after administration in all groups. ABX464 was rapidly and substantially metabolized into ABX464-NGlc. The C_{max} of ABX464-NGlc was observed approximately 4 h post-dose and was about 160-fold higher than that of the parent with a much longer $t_{1/2}$ (90–110 h). The ratio of metabolite to parent drug was consistent across the complete dose range.

Conclusions: These studies confirmed that ABX464 is well tolerated and rapidly and substantially metabolized into ABX464-NGlc in human subjects.

Introduction

More than 40 million people have died from HIV-1-related causes globally since the emergence of HIV, and over 30 million people are still infected with the virus.[1]

Since the introduction of combination ART (cART) for HIV infection, millions of AIDS-related deaths have been prevented in the recipients of this therapy.[2,3] Although cART effectively suppresses HIV replication to undetectable levels in plasma and has led to a major reduction in HIV-related mortality and morbidity, HIV still cannot be cured.[4] Life-long cART is required to keep HIV-1 infection under control. This is due to the existence of HIV reservoirs in some long-lived cell populations that harbour integrated latent HIV provirus, as well as the persistence of HIV in anatomical reservoirs.[5–8] Interrupting therapy results in the virus rapidly rebounding to pre-treatment levels.[9]

Even with the major successes of cART, there are some reports that full life expectancy for HIV-1-infected persons has not been restored.[10,11] Multiple studies have demonstrated that people living with HIV are at increased risk of cardiovascular disease, malignancy and a range of other disorders,[12–15] possibly associated with the persistent inflammation associated with low-level virus persistence.[16,17]

Life-long therapy also has major challenges associated with cumulative toxicities from long-term therapy and the increased potential for drug resistance associated with continuous and expanded usage. Achieving either a functional cure (long-term control of HIV in the absence of cART) or a sterilizing cure

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Table 1. Demographic and baseline characteristics

	ABX464 dose (mg)				
	50	100	150	200	Total
Number of subjects	6	6	6	6	24
Age (years)					
mean (SD)	34.0 (6.0)	36.2 (5.7)	38.7 (11.8)	33.0 (8.6)	35.5 (8.1)
median	34.5	37.0	39.0	33.5	37.0
minimum; maximum	25.0; 42.0	28.0; 43.0	19.0; 54.0	20.0; 45.0	19.0; 54.0
Weight (kg)					
mean (SD)	73.9 (8.0)	78.5 (3.6)	77.4 (6.3)	77.8 (7.6)	76.9 (6.4)
median	73.3	79.9	77.2	79.3	77.9
minimum; maximum	64.0; 85.0	72.0; 81.5	70.5; 86.4	64.3; 85.5	64.0; 86.4
BMI (kg/m^2)					
mean (SD)	24.0 (1.8)	24.8 (1.0)	24.5 (1.4)	23.9 (2.4)	24.3 (1.7)
median	23.6	25.1	24.3	24.7	24.6
minimum; maximum	21.8; 26.8	23.0; 25.6	22.7; 27.0	19.2; 25.9	19.2; 27.0
Tobacco habits					
non-smoker	6 (100.0%)	5 (83.3%)	3 (50.0%)	2 (33.3%)	16 (66.7%)
smoker: $\leq$10 cigarettes/day	0 (0.0%)	1 (16.7%)	3 (50.0%)	4 (66.7%)	8 (33.3%)

(elimination of all HIV-infected cells) remain important therapeutic objectives.[10]

There are different classes of drugs currently licensed to treat HIV infection. None of these drugs can eliminate virus reservoirs and all are subject to development of drug-resistant variants.[8] ABX464 is a first-in-class chemical entity with a novel mechanism of activity in that it modulates viral RNA splicing events.[18] RNA splicing is an essential step required for production of viral infectious particles. A balanced production of spliced and unspliced viral RNA is essential for virus replication.[19,20] Spliced viral RNA encodes a range of regulatory proteins including the Rev and Tat proteins, which are essential for viral gene expression in infected cells.[21–23] Unspliced viral RNA encodes at a later stage of infection the Env, Gag and Pol structural proteins, and following transport from the nucleus, unspliced RNA forms the viral RNA genome, which is encapsidated to form infectious virus particles.[24]

This unique feature of the HIV replication cycle has been utilized to generate a compound with a unique mechanism of viral replication inhibition. This inhibition is achieved by promoting 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 targets the interaction of Rev with cellular ribonucleoprotein complexes, an interaction that is an essential step for virus replication, and due to this specificity does not impact normal cellular splicing.[18,24,25]

ABX464 has been demonstrated to be effective in inhibiting replication of different HIV subtypes in PBMCs and macrophages and did not induce any drug resistance during up to 24 weeks of treatment *in vitro*. ABX464 also substantially reduced virus replication in two humanized mouse models infected with HIV. More importantly, while viral load increased dramatically within 2 weeks of terminating cART treatment in control animals, a substantially lower virus rebound was observed after termination of therapy in the ABX464-treated animal group. This antiviral effect was sustained over the full 6 weeks of virus load measurements after treatment termination.[18]

ABX464 is a strong candidate for clinical development. It has a novel mechanism of activity in that it blocks viral gene expression in cells that are already infected. ABX464 may have the potential to neutralize virus reservoirs with the objective of providing a functional or sterilizing cure for HIV infection.

A first-in-man study was conducted in healthy subjects to determine pharmacokinetic (PK) and safety profiles of a single ascending oral dose of ABX464.

Methods

Ethics

The study (Protocol No. ABX464VS1) was approved by the independent ethics committee (Sud-Méditerranée III, France, Approval reference: 2014.01.05) and by the French Health Authorities (ANSM, Agence nationale de sécurité du médicament et des produits de santé, Approval Reference: 14001A-41). The study was conducted between March 2014 and July 2014 in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Written informed consent was obtained from all study participants. The study was registered at https://www.clinicaltrials (NCT02792686).

Study population

Twenty-four male subjects were screened and as all were eligible, six subjects were assigned to each of the four dose groups. No additional methods were employed to reduce potential bias. All subjects were HIV uninfected and in good health on the basis of medical history, physical examination, vital signs, ECG and routine laboratory safety tests. The subjects were aged from 19 to 54 years old, had BMIs of 19.2–27 kg/m^2 and were non-smokers

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Table 2. Number of occurrences [*n* (%)] of TEAEs tabulated by system organ class and preferred term and classified by severity

			ABX-464 dose (mg)				
System organ class	Preferred term	Severity	50 ($n = 2$)	100 ($n = 5$)	150 ($n = 3$)	200 ($n = 9$)	total ($n = 19$)
Gastrointestinal disorders	any term	mild	0 (0%)	3 (60%)	0 (0%)	3 (33.3%)	6 (31.6%)
		moderate	0 (0%)	0 (0%)	0 (0%)	2 (22.2%)	2 (10.5%)
	nausea	mild	0 (0%)	3 (60%)	0 (0%)	2 (22.2%)	5 (26.3%)
	vomiting	mild	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	1 (5.3%)
		moderate	0 (0%)	0 (0%)	0 (0%)	2 (22.2%)	2 (10.5%)
Nervous system disorders	any term	mild	2 (100%)	2 (100%)	2 (66.7%)	4 (44.4%)	10 (52.6%)
		moderate	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	1 (5.3%)
	headaches	mild	2 (100%)	2 (100%)	2 (66.7%)	4 (44.4%)	10 (52.6%)
		moderate	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	1 (5.3%)

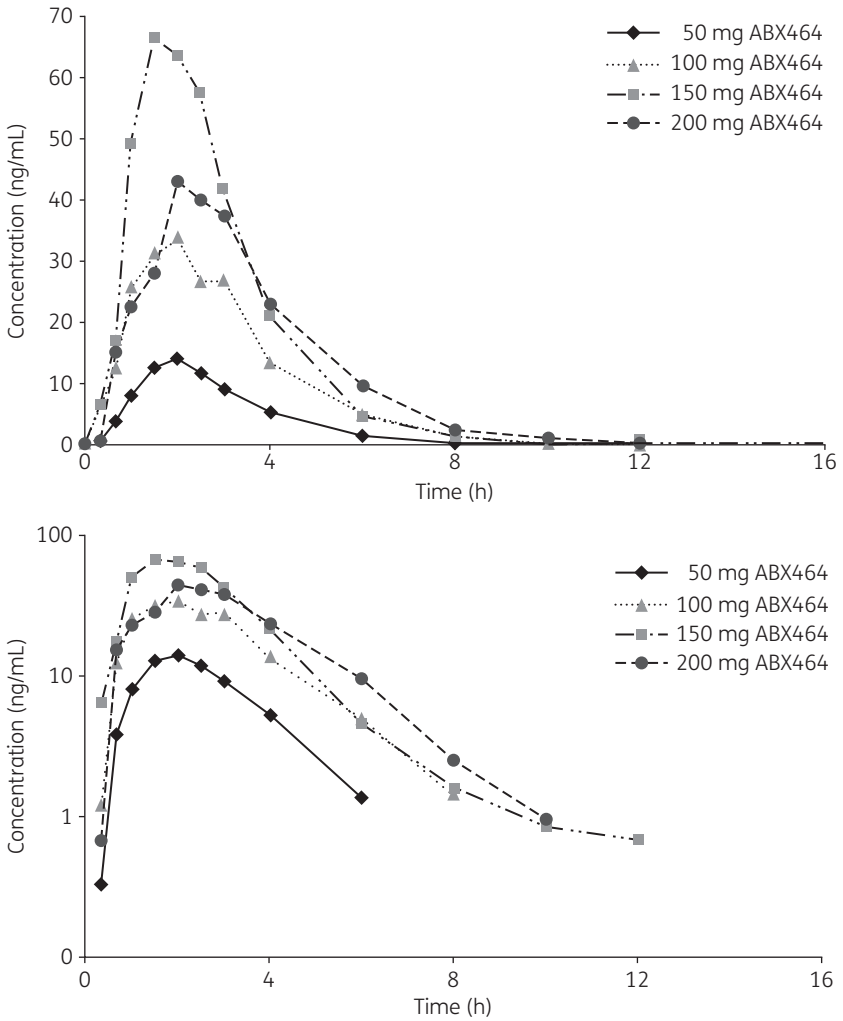

Figure 1. Mean ABX464 plasma concentrations versus time (from 0 to 16 h) after a single oral administration of 50, 100, 150 or 200 mg ABX464 (top figure: natural scale; bottom figure: semi-log scale).

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or light smokers of <10 cigarettes per day. Subjects were included after having given their written informed consent.

Study design

This study was an open label, parallel group, single ascending dose, exploratory study performed at a single site (Centre Cap, Montpellier, France). Six subjects per dose group were enrolled into one of four groups with escalating doses of ABX464 (50, 100, 150 and 200 mg). For each dose group, a first subject was treated, if no adverse event (AE) occurred, a second subject was dosed 1 h later. The four last subjects were dosed the day after if no clinically significant AE occurred. Escalation to the following dose level was decided after review of PK and safety data (laboratory results, ECG, vital signs and AEs) by company representatives and Centre Cap's pharmacologist.

A screening visit was performed within 3 weeks prior to treatment including physical examination, medical history, serology [hepatitis C virus (HCV), hepatitis B virus and HIV], urine drug screen, laboratory test, urinalysis, vital signs and ECG. Subjects were hospitalized from the day prior to dosing until the morning of day 2. The consumption of tobacco, alcoholic beverages, caffeine or xanthine-containing products, as well as grapefruit or grapefruit juice, was prohibited from 48 h prior to dosing until 48 h post-treatment.

A single oral dose of ABX464 (50, 100, 150 or 200 mg) was administered by site personnel with 200 mL water on the morning of day 0 after overnight fasting. On day 10, a complete follow-up visit was performed. Follow-up visits were planned on day 24 and day 45 to track the elimination of ABX464 and its metabolite [ABX-464-*N*-glucuronide (ABX464-NGlc)]. Three subjects were eliminated from the study as they did not perform the follow-up visit on day 45 (two in the 50 mg group and one in the 100 mg group).

Safety assessments consisted of vital signs, ECG and physical examination performed on day −1, day 0, day 1, day 2 and day 10; laboratory tests and urinalysis performed on day −1, day 2 and day 10. AEs were monitored throughout the study. Persons evaluating AEs were not blinded to assignment. Analysis of PK samples was done in a blinded fashion.

Endpoints

The objectives of this study were to determine PK profiles of ABX464 and ABX464-NGlc and to assess the safety of four single oral doses of ABX464 (50, 100, 150 and 200 mg).

PK analysis

For assessment of ABX464 and ABX464-NGlc plasma levels, 4 mL blood was collected into lithium heparin tubes before administration and at 0.33, 0.66, 1, 1.50, 2, 2.50, 3, 4, 6, 8, 10, 12, 24, 36, 48, 240, 576 and 1080 h post-dose. Tubes were centrifuged within 30 min at 4 °C at 3500 rpm for 15 min. Collected plasma was transferred to two cryotubes and stored at −20 °C.

Plasma samples were analysed for ABX464 and ABX464-NGlc using validated bioanalytical methods by Atlanbio (Saint-Nazaire, France) according to Good Laboratory Practice (GLP).

PK parameters were calculated by non-compartmental analysis (NCA), using Phoenix® WinNonlin® (Pharsight Corporation) running on a personal computer. The measured PK parameters were, for ABX464 and ABX464-NGlc, maximum concentration (C_{max}), time to maximum concentration (T_{max}), 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_e), AUC from time 0 to infinity ($AUC_{0-\infty} = AUC_{0-t} + C_t/k_e$, where C_t was the measured concentration at time of the last quantifiable concentration), apparent terminal elimination half-life ($t_{1/2} = \ln 2/k_e$) and for ABX464 only: apparent total clearance ($CL/F = dose/AUC_{0-\infty}$) and apparent volume of distribution ($V/F = CL/F/k_e$).

Statistical analysis

All subjects were analysed both in the safety and PK parts of the study as assigned to treatment. No subgroup analyses were carried out and no missing data was included. Descriptive statistics were performed on demographic data, vital signs (blood pressure, pulse rate and respiratory rate), clinical laboratory parameters, ECG parameters (QT, QTcB, PR, QRS 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 version 3.2.3 build 340 and RB version 3.2.10 build 340).

The hypothesis that AUC and C_{max} are dose proportional was planned to be formally tested using a power model approach. Assessment of the dose proportionality was performed for the complete dose range. For the four dose levels investigated and each compound, AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} values were analysed for dose proportionality using analysis of variance techniques.[26,27]

Prior to the analysis, the assumption of a linear relationship between the log AUC (C_{max}) and log-dose was tested using analysis of variance by partitioning the sums of squares for dose into those for linearity and departures from linearity. If departures from linearity were significant, then the hypothesis of dose proportionality was rejected and the power model analysis was not performed. The proportionality was tested at a 5% significance level.

Results

Baseline characteristics and patient disposition

Twenty-four healthy male subjects aged from 19 to 54 years and with mean BMIs of 19.2–27 kg/m^2 were included in the study (six in each group) and received the treatment as planned in the protocol. Demographic and baseline characteristics are included in Table 1. Baseline characteristics did not differ between groups to an extent that they could influence results. No statistical methods were applied to adjust for potential baseline differences. Three subjects were eliminated from the study as they did not perform the follow-up visit on day 45 (two in the 50 mg group and one in the 100 mg group). Subjects lost to follow-up did not have different baseline characteristics to the rest of the study population. All six subjects from each study group were included in the safety and PK analysis.

At screening, no clinically significant abnormalities were detected on physical examination, laboratory tests, urinalysis, vital signs and ECG parameters. No significant deviations were reported during the study; however, it was noted that eight subjects had a QTcB >430 ms before dosing. These values were considered as not clinically significant. All the enrolled subjects were analysed in the safety and PK analysis set.

Safety and tolerability

Table 2 shows the number of treatment-emergent AEs (TEAEs) reported in this study. Overall, a total of 13 subjects out 24 reported 19 AEs of mild or moderate intensity. All these AEs occurred within the 48 h following drug administration. AEs consisted of headache (11 cases reported by 10 subjects), nausea (5 cases reported by 4 subjects) and vomiting (3 cases reported by 3 subjects). Up to

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Table 3. PK parameters of ABX464 in male subjects after a single oral administration of 50, 100, 150 or 200 mg ABX464

Dose (mg)		C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
50	number of subjects	6	6	6	6	6
	mean	14.36	1.75	40.78	42.04	1.09
	SD	8.65	1.50–2.50	22.07	22.05	0.23
	CV%	60	22	54	52	21
	GM	12.38	1.80	36.50	37.91	1.07
100	number of subjects	6	6	6	6	6
	mean	37.78	1.75	111.17	113.57	1.41
	SD	23.26	1.00–4.00	72.76	72.52	0.92
	CV%	62	52	65	64	65
	GM	32.02	1.82	95.15	98.13	1.24
150	number of subjects	6	6	6	5	5
	mean	72.46	1.75	203.71	189.29	6.85
	SD	53.19	1.50–2.50	182.45	202.82	9.46
	CV%	73	22	90	107	138
	GM	50.38	1.80	126.16	109.86	3.50
200	number of subjects	6	6	6	4	4
	mean	53.15	2.00	159.10	201.16	1.55
	SD	58.62	0.66–4.00	163.30	187.91	0.37
	CV%	110	59	103	93	24
	GM	24.87	1.78	91.84	127.59	1.51

[a]Median and minimum–maximum.

150 mg, all AEs consisted of headache and nausea of mild or moderate intensity. Headaches appeared between 1 and 9 h after dosing and lasted from 30 min to 11 h and 30 min. At the highest tested dose level (200 mg), 3 out of 6 subjects experienced one episode of vomiting of mild to moderate intensity between 4 and 9 h after dosing. In one subject nausea was reported just before vomiting. Nine subjects received concomitant medication to treat AEs, mainly paracetamol. There were no serious AEs (SAEs), no deaths and no subjects withdrew from the study due to AEs.

Mean values of laboratory, vital signs and ECG parameters remained within normal ranges throughout the study duration and no significant changes from baseline were observed. Sporadic abnormal individual values were reported but the extent of abnormality was always very limited and did not suggest any impact of drug administration on biochemistry, haematology or on cardiovascular activity.

Up to 150 mg, ABX464 was very well tolerated. With regard to the aetiology of vomiting, this did not appear as a limiting side effect and thus was not considered as a restriction to the dose escalation.

PK

All subjects were exposed to ABX464 after administration. The mean PK parameters for ABX464 after a single oral administration of 50–200 mg are reported in Table 3 and mean ABX464 plasma concentration–time profiles are shown in Figure 1. C_{max} was observed between 1.75 and 2 h after dosing (ranging from 0.66 to 4 h) in all groups with mean values ranging from 14 to 72 ng/mL. AUC_{0-t} ranged from 41 to 204 ng·h/mL. Mean values of half-life were comparable for three dose levels out of four (50, 100 and 200 mg) with values between 1.1 and 1.6 h, whereas it was markedly higher for 150 mg (6.85 h) with an important variability. It was noted in this dose group that one subject had a very long $t_{1/2}$ (nearly 24 h).

Inter-individual variability as expressed by coefficient of variation (CV%) tended to increase with 150 mg and 200 mg, reaching 90%–107% for AUCs.

Overall, geometric mean (GM) of rate and extent of exposure of ABX464 did not increase consistently with the dose. When the ABX464 dose was increased by factors of 2, 3 and 4, C_{max} increased by 2.6, 4.1 and 2.0, AUC_{0-t} increased by 2.6, 3.5 and 2.5, and $AUC_{0-\infty}$ increased by 2.6, 2.9 and 3.4, respectively. It could be noted that two subjects had extremely low ABX464 plasma concentrations at the 200 mg dose; this observation could not be ascribed to vomiting experienced by these subjects since the vomiting episodes were reported at post-dose times higher than the observed T_{max}. Moreover, the inter-variability observed at the two higher dose levels was quite high and certainly contributed to the lack of dose proportionality over the complete dose range. Formal assessment of dose proportionality indicated a significant departure from linearity, supporting the comments drawn from observed data.

ABX464 was rapidly and substantially metabolized into ABX464-NGlc after a single oral administration, regardless of the dose. The first quantifiable ABX464-NGlc concentration was generally observed at 40 min post-dose for all dose levels (20/24 subjects). Plasma concentrations were markedly higher than those of the parent drug. The ABX464-NGlc plasma concentration–time profile is shown in Figure 2 and the mean PK

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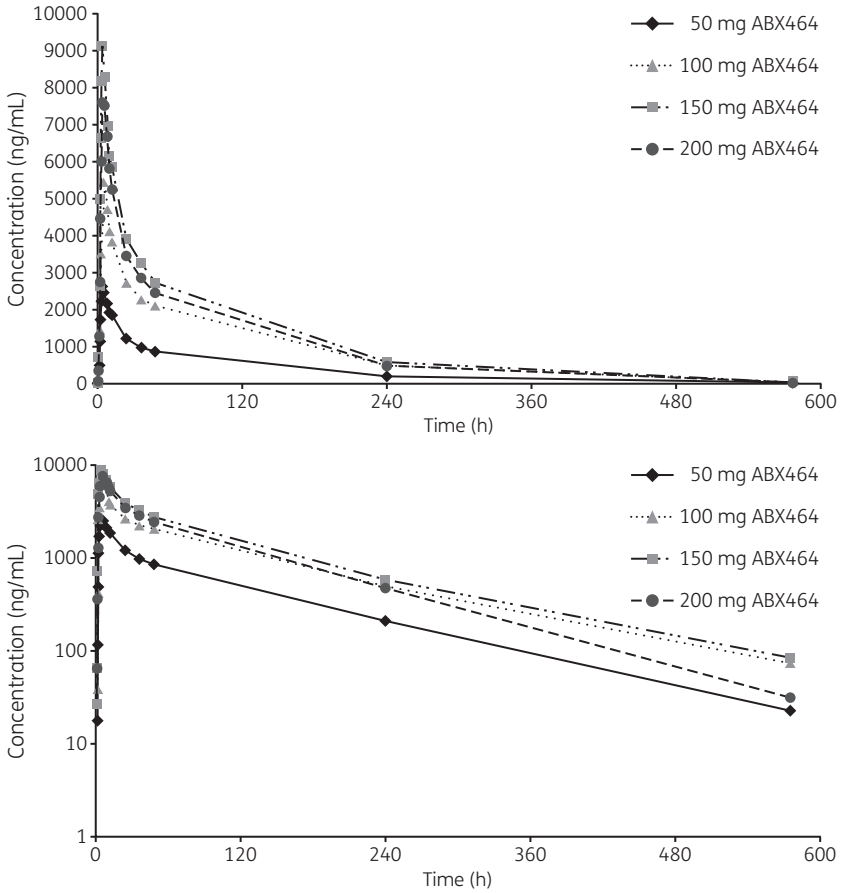

Figure 2. Mean ABX464-NGlc plasma concentrations versus time after a single oral administration of 50, 100, 150 of 200 mg ABX464 (top figure: natural scale; bottom figure: semi-log scale).

parameters for ABX464-NGlc after single oral administrations of 50–200 mg ABX464 are reported in Table 4. Median T_{max} was comparable across dose levels, varying from 4 to 6 h post-dose with a very low inter-individual variability (3–6 h). ABX464-NGlc C_{max} and AUC_{0-t} values ranged from 2627 to 9243 ng/mL and 208811 to 659186 ng·h/mL, respectively. Inter-individual variability of C_{max} and AUCs tended to increase with ABX464 doses, being <50% for the two lower dose levels and reaching 70%–80% at 200 mg.

The $t_{1/2}$ was roughly comparable in terms of GM values and variability from 50 to 200 mg with mean values of between 88 and 111 h.

Considering the complete dose range, no clear trend could be elicited in the GMs of rate and extent of exposure of ABX464-NGlc. However, between 50 and 150 mg, C_{max} and AUCs tended to increase with dose. When the ABX464 dose increased by a factor of 2, 3 and 4, GM C_{max} increased by 2.1, 3.3 and 2.3, GM AUC_{0-t} increased by 2.4, 2.9 and 2.2, and GM $AUC_{0-\infty}$ increased by 2.4, 2.8 and 2.2. As seen for the parent drug, the low ABX464-NGlc plasma concentrations observed in two subjects of the 200 mg cohort emphasized the non-dose-proportional trend. Formal assessment of dose proportionality confirmed these observations and was in line with the results obtained for the parent drug.

The ratios of metabolite to parent drug relationship supported the very high rate of biotransformation of ABX464 into ABX464-NGlc since mean ratios of $AUC_{0-\infty}$ varied from 3500 to 6600, depending on the dose level. Despite the wide inter-individual variability, the C_{max} and $AUC_{0-\infty}$ ratios can be considered comparable across dose levels. However, regarding the extent of biotransformation into ABX464-NGlc, no clear difference over the studied dose range was observed.

Discussion

The objective of this first-in-man study was to determine the safety profile, as well as the PK parameters, of ABX464 and its main metabolite after single-dose administration of 50–200 mg ABX464. At this stage in the clinical development programme, before safety had been established in human trials, it was not considered appropriate to include HIV-infected subjects or subjects coinfected with HCV in this first-in-man study. 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 analysed as the study was done with low subject numbers ($n = 24$), in the 18–55 year age group, as is standard for such first-in-man studies. Future studies are being designed to include females, HIV- and HCV-infected subjects and other age groups.

The product was safe and well tolerated in both studies; no product-related SAEs occurred and no AEs led to premature

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Table 4. Summary of descriptive statistics of ABX464-NGlc PK parameters after a single oral administration of 50, 100, 150 or 200 mg ABX464

Dose (mg)		C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
50	number of subjects	6	6	6	6	6
	mean	2627	4.00	208811	211777	97
	SD	754	4.00–4.00	86273	90392	20
	CV%	29	0	41	43	21
	GM	2536	4.00	196038	198171	96
100	number of subjects	6	6	6	6	6
	mean	5717	4.00	498879	505290	111
	SD	2150	4.00–6.00	206401	203393	11
	CV%	38	19	41	40	10
	GM	5403	4.28	467829	475564	111
150	number of subjects	6	6	6	6	6
	mean	9243	4.00	659186	664064	99
	SD	4622	3.00–4.00	398824	401717	28
	CV%	50	14	61	60	28
	GM	8273	3.63	559712	563291	96
200	number of subjects	6	6	6	6	6
	mean	7907	6.00	558712	560431	90
	SD	6167	4.00–6.00	395065	396155	19
	CV%	78	14	71	71	21
	GM	5896	5.61	436350	438116	88

[a]Median and minimum-maximum.

discontinuation. No clinically significant abnormal results appeared in physical examinations, laboratory test results, vital signs and ECGs in either study. The most common ABX464-related TEAEs in both studies were headaches and gastrointestinal disorders (vomiting and nausea). In this first-in-man study, 13/24 subjects reported AEs of mild to moderate severity, with headache being the most frequently reported AE. Review of the rate of headaches suggested this effect could be a first-dose effect, tending to disappear in case of repeated treatment. Nausea was also reported by 5 subjects, with cases of vomiting occurring in 3/6 subjects at the highest dose (200 mg) used.

These clinical data are consistent with preclinical data generated in non-human primates and dogs where the gastrointestinal tract was demonstrated to be the main target organ of ABX464 toxicity. Also, due to the acceptable level of tolerance demonstrated in these clinical studies, the maximum tolerated dose was not considered to have been reached and remains to be determined.

The PK data collected showed that after single oral administration of 50, 100, 150 and 200 mg, ABX464 was absorbed and substantially metabolized into ABX464-NGlc in humans. Extensive *in vitro* metabolite profiling has been conducted on cryopreserved human hepatocytes, which showed that, *in vitro*, only an *N*-glucuronide metabolite could be detected. This pattern of metabolism was also seen in studies with mice and non-human primates.

Maximum concentration of ABX464 was observed approximately 2 h after dosing in all groups, with mean values ranging from 14 to 72 ng/mL and with a $t_{1/2}$ of ∼1–2 h in the great majority of the subjects. Its metabolite, ABX464-NGlc, as observed in preclinical studies, exhibited markedly higher blood concentrations, ∼160-fold higher than for the parent drug, and had a much longer $t_{1/2}$ (90–110 h). ABX464-NGlc C_{max} was observed around 4 h post-dose with a low variability.

These results may be significant for the effectiveness of ABX464 as an antiviral compound. It has been reported that ABX464-NGlc was as efficient as ABX464 *in vitro* in inhibiting HIV-1 replication in primary macrophages,[18] strongly suggesting that it might also induce viral replication inhibition in humans. Considering its relatively long half-life, which would lead to a significant accumulation, ABX464-NGlc may prolong and amplify ABX464 antiviral activity. This antiviral activity of ABX464-NGlc has only been seen in macrophages and not in T cells.[18] However, it has been reported that infected macrophages may be at least one of the key viral reservoirs that mediate viral rebound after cessation of ART.[28–30] As such, the generation of this metabolite with a substantially longer half-life may support elimination of virus reservoirs, which are not impacted by currently available anti-HIV therapies. However, it must be emphasized that the extended half-life of the metabolite cannot alone explain the substantial viral load reduction in HIV-infected mice, followed by a long-lasting effect on the viral load after ABX464 treatment termination. These long-lasting effects of ABX464 are possibly also a result of immune-mediated mechanisms, which are currently under evaluation.

For ABX464 and ABX464-NGlc, the relationship between ABX464 dose and exposure was approximately linear between 50 and 150 mg, both C_{max} and AUCs increasing in a nearly dose-proportional manner. C_{max} and AUCs, however, were found to be almost unchanged between 150 and 200 mg, although it should be kept in mind that two subjects had unexpectedly low drug and

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metabolite blood levels when receiving 200 mg ABX464. As such, a formal dose proportionality assessment was not conclusive. The rate of biotransformation of ABX464 into ABX464-NGlc was consistent across the complete dose range but inter-individual variability prevented definite conclusions.

These studies provide the first data in humans on the safety, tolerability, bioavailability and metabolism of ABX464. These studies only included male subjects but the PK and toxicology studies carried out in non-human primates have included both males and females. No appreciable differences between genders were observed in these studies.

This is a novel anti-HIV compound with a unique mechanism of activity. Based on the available pre-clinical data this compound may have the potential, either as a monotherapy or more likely in combination with other classes of anti-HIV drugs, to have a substantial anti-HIV effect. It may possibly even have potential as a curative therapy. The data obtained from these studies warrant further investigation of this compound in HIV-infected subjects. A Phase IIa dose escalation study to investigate safety, PK and viral kinetics of ABX464 in untreated patients with HIV infection is currently ongoing and will provide the first data on the anti-HIV effects of ABX464 in humans. Additional human studies are also ongoing or being planned to investigate the safety profile and anti-HIV effects of ABX464 in combination with licensed HIV antivirals.

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Transparency declarations

D. S., J.-M. S., P. G. and H. J. E. are ABIVAX employees and own stock in ABIVAX. P. N. B. and R. L. M. perform consultancy services for ABIVAX. R. R. was the principal investigator of the study and received consultancy fees. J. T. is a member of a collaborative laboratory that has received financial support from ABIVAX. Employees of ABIVAX (who were the main funders for the study) played a decision-making role in the design, execution, analysis and reporting of the study.

Author contributions

The study design was provided by D. S., J. T., J.-M. S., H. J. E. and R. L. M. The study was conducted in Centre Cap under the supervision of R. R. Study analyses and manuscript writing was provided by P. N. B., P. G., D. S. and J. T.

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