Poster
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Early Evidence of Antiviral Activity and Safety of ABX464 in HIV Treatment-Naïve Patients

Didier Scherrer[1], Jean-Marc Steens[1], Supparatpinyo Kuanchai[2], Ratanasuwan Winai[3], Kiat Ruxrungtham[4], Regine Rouzier[5], Jamal Tazi[6], Paul Gineste[1], Hartmut Ehrlich[1], Robert Murphy[7]

[1] ABIVAX, Paris, France; [2] Chiang Mai University, Chiang Mai, Thailand; [3] Siriraj Hospital, Bangkok, Thailand; [4] HIV-NAT, Chulalongkorn University Hospital, Bangkok, Thailand; [5] Cap Research, Phoenix, Mauritius; [6] University of Montpellier, Montpellier, France; [7] Northwestern University Feinberg School of Medicine, Chicago, USA

ABIVAX
5, rue de la Baume
75008 Paris, France
E-mail: info@abivax.com
Tel.: +33(0)1 53 83 08 41
www.abivax.com

Background

- ABX464 is a first-in-class antiviral drug candidate for the treatment of patients with HIV-infection. It is an orally available small molecule that blocks HIV replication through an entirely novel mechanism, inhibition of Rev activity.
- Preclinical data in humanized mice showed that ABX464 monotherapy had an antiviral effect, which was sustained after treatment interruption.[1]
- A prior food-effect study demonstrated a 3-fold increase in parent drug exposure when administered with food without a significant impact on the active glucuronide metabolite.[2]

Objectives

ABX464-003 is a randomized, multi-center, double-blind, placebo-controlled, ascending dose-ranging study in treatment-naïve HIV-1 infected patients.

Primary endpoint:

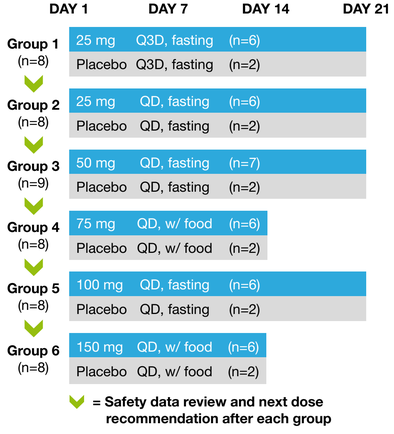
- To evaluate the safety and tolerability of repeated oral administrations of ABX464.

Secondary endpoint:

- To evaluate pharmacokinetics and viral kinetics of ABX464 in untreated patients with HIV infection.

Methods

- Four centers in Thailand and one in Mauritius were included in the study and conducted local ethics reviews.
- Patients were enrolled after confirmation of HIV infection and no history of prior antiretroviral therapy.
- Patients were randomized into successive cohorts of 8 patients where 6 received 14 or 21 days of ABX464 and 2 received placebo.
- Dose escalation decisions were validated by an independent Data Safety Monitoring Board (DSMB).
- The initial group received 25 mg every 3 days. Successive groups received 25, 50, 75, 100, and 150 mg QD. The 25, 50, and 100 mg groups took drug fasting for 21 days, the 75 and 150 mg groups took drug with food for 14 days.



Results

Table 1. Baseline Demographics

	Placebo (n=12)	25 mg Q 3 days (n=6)	25 mg QD (n=6)	50 mg QD (n=7)	75 mg QD (n=6)	100 mg QD (n=6)	150 mg QD (n=6)	Total (N=49)
Median Age, yrs	30.0	42.0	36.5	32.0	29.5	45.0	22.5	31.0
Male, n (%)	8 (66.7)	3 (50.0)	1 (16.7)	2 (28.6)	3 (50.0)	3 (50.0)	5 (83.3)	25 (51.0)
Median Baseline HIV-1 RNA, log_{10} copies/mL	4.76	4.83	4.74	5.04	4.55	4.01	4.47	4.65
Median Baseline CD4 Cells, count/mm^3	409	485	385	420	577	315	549	470

Table 2. Most Frequent Adverse Events (>10%) by Group

	Placebo (n=12)	25 mg Q 3 days (n=6)	25 mg QD (n=6)	50 mg QD (n=7)	75 mg QD (n=6)	100 mg QD (n=6)	150 mg QD (n=6)	Total (N=49)
Total Adverse Event, n (%)	7 (58.3)	3 (50.0)	2 (33.3)	4 (57.1)	6 (100.0)	6 (100.0)	6 (100.0)	34 (69.4)
Headache, n (%)	4 (33.3)	1 (16.7)	1 (16.7)	3 (42.9)	6 (100.0)	5 (83.3)	6 (100.0)	26 (53.1)
Nausea, n (%)	1 (8.3)	1 (16.7)	0 (0.0)	1 (14.3)	4 (66.7)	0 (0.0)	6 (100.0)	13 (26.5)
Vomiting, n (%)	0 (0.0)	1 (16.7)	2 (33.3)	1 (14.3)	4 (66.7)	0 (0.0)	4 (66.7)	12 (24.5)

Table 3. Correlation of ABX464 vs Adverse Event Incidence

	Method (Max of Cmax vs Average of Cmax)	Type of Adverse Events	Cmax vs Number of AEs Spearman Correlation Coefficient (95%)	Cmax vs Duration (days) of AEs Spearman Correlation Coefficient (95% CI)
ABX464	AVG	Headache	0.58 (0.26 to 0.90)	0.56 (0.29 to 0.83)
	AVG	Nausea/Vomiting	0.57 (0.31 to 0.83)	0.63 (0.34 to 0.92)
	MAX	Headache	0.52 (0.14 to 0.90)	0.47 (0.08 to 0.85)
	MAX	Nausea/Vomiting	0.57 (0.28 to 0.85)	0.62 (0.31 to 0.92)

Safety

- The most common adverse events noted were headache, nausea, and vomiting.
- All events were grade 1 or 2.
- All patients completed at least 14 days of treatment per protocol.
- There were no serious adverse events.

Figure 2. Number of Drug-Related Adverse Events in First 24 Hours in the 150 mg ABX464 Treatment Group

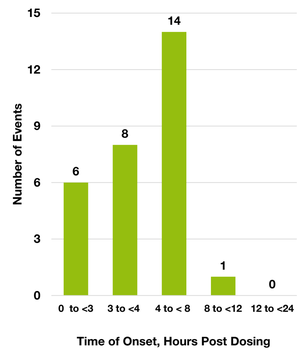
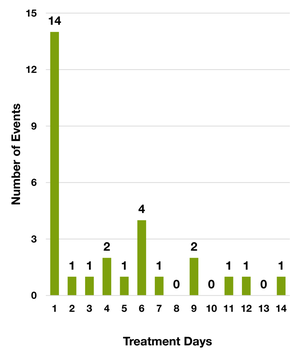


Figure 3. Onset of Adverse Events in the 150 mg ABX464 Treatment Group



Efficacy

Number of ABX464-treated patients who achieved a 0.5 log_{10} reduction in HIV-1 viral load by Day 14:

- **75 mg Group:** 1-of-6
- **100 mg Group:** 2-of-6
- **150 mg Group:** 4-of-6

Figure 4. Change in Viral Load from Baseline in the 150 mg ABX464 Treatment Group

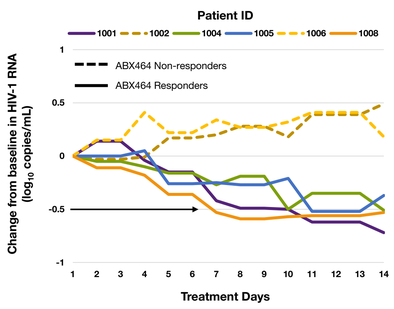


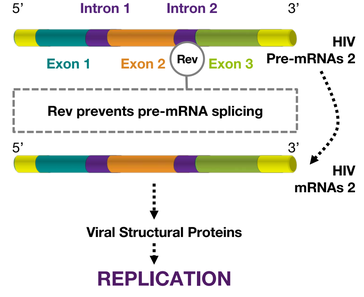
Figure 1. ABX464 Mechanism of Action

Human mRNA Biogensis Requires Splicing

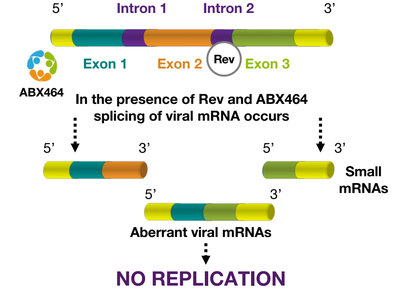
Human mRNA splicing is an editing process of the nascent pre-messenger RNA (pre-mRNA) transcript in which introns are removed.

HIV Requires Unspliced mRNA to Synthesize Structural Proteins

Viral Unspliced mRNA Biogenesis in HIV-infected Cells



Effect of ABX464 on Unspliced mRNA Biogenesis in-HIV Infected Cells



Conclusion

- ABX464 was well tolerated in this first study in treatment-naïve HIV-infected patients.
  - The most common drug-related adverse events were headache, nausea, and vomiting. All occurred within the first 24 hours of dosing and diminished; no event was greater than grade 2.
  - Preliminary PK analysis suggest these events are related to Cmax.
- ABX464 monotherapy showed dose-related antiviral activity with 4-of-6 patients in the 150 mg dose group achieving 0.5 log_{10} reduction by Day 14. Preliminary PK analysis does not differentiate responders versus non-responders.
- These results warrant the further planned development of this novel acting antiretroviral drug.

References

1. Campos et al. *Retrovirology* (2015) 12:30.
2. Data on file.

Acknowledgements

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