

# CXCR4 Antagonism: Proof of Activity with AMD11070



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## Abstract

**Background:**  
The chemokine receptor CXCR4 (X4) is used by HIV as a co-receptor in up to 50% of patients with advanced disease. X4 use is associated with rapid CD4 decline and disease progression. AMD11070 (070) is an orally bioavailable small molecule CXCR4 antagonist and potent inhibitor of HIV replication *in vitro*. The X4 Antagonist Concept Trial (XACT) investigates the safety and activity of 070 monotherapy for 10 days.

**Methods:**  
XACT is a multicenter, dose-finding safety and activity study of 070 in patients with evidence of X4 virus determined by the Monogram Coreceptor Tropism Assay. Ten patients were dosed with 070 as monotherapy twice daily for 10 days (200 mg, n=8; 100 mg, n=2). Patients were treatment naive or at least 14 days without ART. Patients had  $\geq 2000$  X4 relative luminescence units (rlu) and an HIV RNA level of  $\geq 5000$  copies/ml. Tropism (including X4 and R5 rlu), plasma HIV viral load and CD4 level were measured at baseline, day 5 and day 10. The primary endpoints were X4 rlu reduction  $\geq 1 \log_{10}$  and safety. Secondary endpoints included change in levels of CD4 and HIV RNA and pharmacokinetic parameters.

**Amendment:** Clinical development of AMD11070 is currently put on hold pending further preclinical safety assessments.

**Results:**  
Median baseline CD4 and HIV RNA levels were 144 cells/mm<sup>3</sup> and 160,757 copies/ml (n=10). At screening, 9 patients had dual/mixed (D/M) virus and 1 had X4 only. One patient was deemed non-evaluable due to discrepant tropism assay results. Four of 9 patients met the primary endpoint of  $\geq 1 \log_{10}$  reduction in X4 rlu. Among these responders the mean X4 log<sub>10</sub> rlu reduction was -1.56 (median = -1.50). The mean overall change in X4 log<sub>10</sub> rlu (n=9) was -0.71 (median = -0.22). Two of 4 responders showed a tropism switch from D/M to exclusively R5 virus at Day 5, while 1 other responder showed the same switch at Day 10. There were no significant changes in CD4, lymphocyte counts and HIV RNA levels overall (n=9) or just among the responders (n=4). There were no drug-related serious adverse events (AEs) or > grade 2 AEs or lab abnormalities. The most common AEs were mild GI symptoms and headache. PK analysis revealed no correlation between exposure and rlu response.

**Conclusions:**  
Preliminary results have demonstrated the activity of AMD11070 against X4-tropic virus where an X4 rlu reduction of  $\geq 1 \log_{10}$  was observed in 4 of 9 patients. AMD11070 was well tolerated. Further development of this first CXCR4 antagonist, including dose escalation and other preclinical and clinical studies, is ongoing.

## Demographics and Baseline Characteristics

Ten patients were enrolled and completed the study. One patient was deemed non-evaluable due to discrepant tropism assay results.

Race: 6 Caucasian, 2 Hispanic/Latino, 1 black African, 1 mixed white/black  
Sex: 9 males and 1 female

Demographics	
N=10	Median (range)
Age (years)	41 (34 - 50)
Weight (lb)	182.6 (140.4 - 262)
Height (cm)	179.5 (163.5 - 188)

Baseline Characteristics (n=9)\*

N=9	Median (range)
CD4 (cells/ml)	129 (1 -- 336)
HIV copy/ml	166588 (14700 -- 3620225)
X4 (Log <sub>10</sub> rlu)	3.85 (3.20 -- 5.88)
R5 (Log <sub>10</sub> rlu)	4.94 (1.74 -- 5.88)

\*Efficacy Dataset N=9  
One patient was deemed non-evaluable due to discrepant tropism assay results.

## Safety Results

No laboratory abnormalities Grade 1 or higher were observed.

Table 5:  
Safety - Liver Function (n=10)

Pt ID	Entry	ALT (U/L)			AST (U/L)			Bilirubin (mg/dl)			
		Day 5	Day 10	Day 17	Day 5	Day 10	Day 17	Day 5	Day 10	Day 17	
XACT 01	52	40	35	36	47	53	41	36	0.5	0.4	0.4
XACT 02	27	27	33	31	26	26	26	25	0.5	0.4	0.6
XACT 03	41	22	27	33	34	24	23	23	0.7	0.7	0.4
XACT 04	35	30	31	87	46	54	47	91	0.5	0.5	0.4
XACT 05	20	25	30	28	35	34	35	39	0.7	0.6	0.4
XACT 06	34	32	33	32	25	24	22	23	0.6	0.5	0.4
XACT 07	69	44	38	42	48	34	33	38	0.4	0.5	0.3
XACT 08	40	36	33	31	29	25	25	20	0.5	0.7	0.4
XACT 09	11	12	13	14	14	13	15	15	0.4	0.4	0.4
XACT 10	48	25	22	31	55	31	37	52	0.5	0.5	0.4

Non-Responders (patients with <1 log<sub>10</sub> reduction in X4 rlu) are highlighted

Table 6:  
Safety - Summary of All Study Drug Related AE's

Pt ID	AE Terms	Drug-relatedness	Severity
101	Flatulence	Probably Related	Grade 1
103	Headache	Possibly Related	Grade 2
104	Diarrhea	Possibly Related	Grade 1
105	Dizziness	Possibly Related	Grade 1
105	Diarrhea	Probably Related	Grade 1
109	Diarrhea	Possibly Related	Grade 1

--There were no clinically significant out-of-range safety lab findings

## Introduction

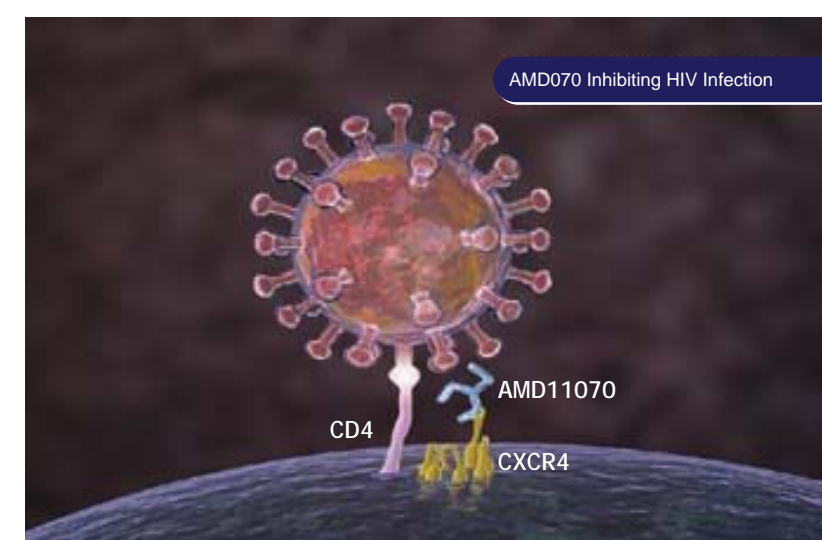
HIV entry into cells is initiated by the binding of the viral envelope protein to the cellular receptor CD4 and a coreceptor, either the CCR5 (R5) or CXCR4 (X4) chemokine receptor. The development of drug resistance and toxicities among the current drug classes have prompted the investigation into novel antiretroviral agents with a unique mechanism of action. Both CCR5 and CXCR4 inhibitors are being evaluated in clinical trials as potential candidates of a new class of HIV entry inhibitors.

CCR5 is the coreceptor used by the majority of the HIV strains (R5-tropic strains). CXCR4 using (X4-tropic) and CCR5/CXCR4 using (Dual-tropic) strains usually emerge later in disease in 30-50% of infected individuals. The presence of X4 virus is strongly associated with CD4 decline and disease progression.

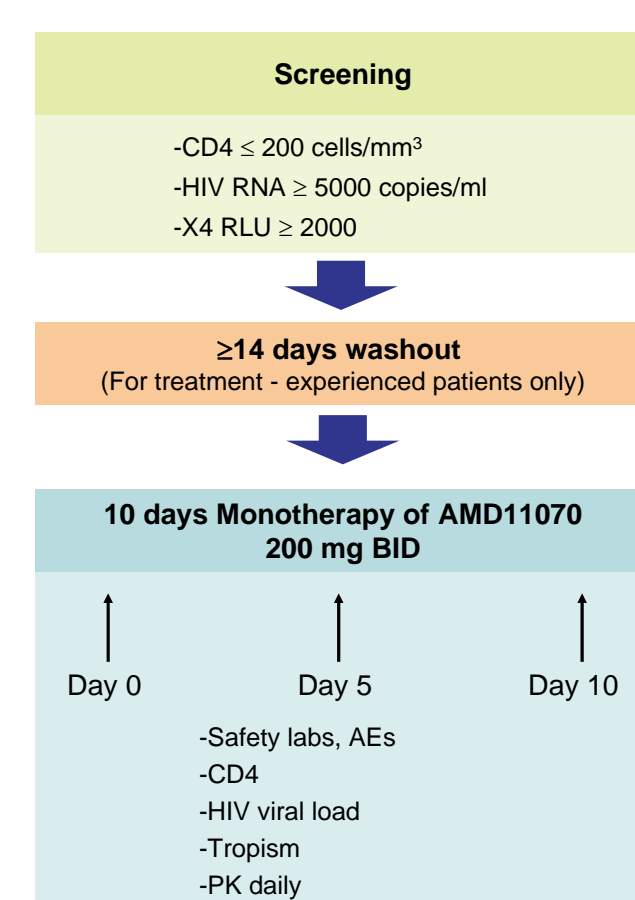
AMD11070 is an orally bioavailable, selective and reversible small molecule CXCR4 inhibitor. It has been shown to inhibit HIV entry in PBMC and other cell lines *in vitro*. In addition, *in vitro* assays also demonstrated that it inhibits the binding of the natural chemokine ligand, SDF-1 $\alpha$ , to CXCR4 and inhibits SDF-1 $\alpha$  induced signaling mechanisms.

In the AMD11070-XACT study, we evaluated the safety and antiviral activity of AMD11070 given as a monotherapy for 10 days in HIV-infected patients who harbor X4-tropic virus. The primary endpoints are the proportion of patient who has  $\geq 1 \log_{10}$  rlu reduction in X4-tropic virus and the changes in X4 rlu from baseline to Day 10. We also assessed the relationship between pharmacokinetic measures and viral response, the changes in CD4 count, HIV plasma viral load, WBC and CD34 count.

Figure 1  
AMD11070 Inhibition of HIV Entry



## Methods - Study Design



## Study Endpoints

Primary Efficacy Endpoints:

- Safety
- Proportion of patients with  $\geq 1 \log_{10}$  X4 rlu reduction
- Changes in X4 rlu from baseline to Day 10

Secondary Efficacy Endpoints:

- Change in CD4 level
- Change in HIV RNA level
- PK Parameters

## Efficacy Results

Efficacy Dataset N=9

Table 1:  
Virologic Response- X4 RLU

Pt ID	screening	Log X4 RLU				$\Delta$ X4 Day 1/Day 10	$\Delta$ X4 Day 1/Nadir
		0	5	10	17		
XACT 01*	5.69	5.57	5.41	5.61	6.04	6.20	0.04
XACT 02*	5.90	3.85	1.92	1.95	2.11	3.19	-1.90
XACT 03	5.21	4.84	4.87	4.62	3.24	na	-0.22
XACT 04	3.44	3.82	2.51	3.10	na	na	-0.72
XACT 05	5.25	5.88	5.83	5.76	5.76	5.75	-0.12
XACT 06	4.88	5.18	5.00	5.41	4.81	5.49	0.23
XACT 07	4.10	3.56	4.24	3.34	3.88	3.76	-0.22
XACT 08	na	3.61	3.00	1.98	2.06	3.29	-1.63
XACT 09	3.90	3.20	2.10	1.83	3.36	3.11	-1.37
Median (all)	3.85	4.24	3.34	3.62	3.76	-0.22	
Mean (all)	4.39	3.88	3.73	3.91	4.40	-0.66	
SD (all)	0.99	1.50	1.64	1.52	1.36	0.78	
Median (Resp)	3.71	2.31	1.97	2.11	3.19	-1.50	
Mean (Resp)	3.62	2.39	2.22	2.51	3.19	-1.40	
SD (Resp)	0.30	0.48	0.59	0.74	0.09	0.50	

Non-Responders (patients with <1 log<sub>10</sub> reduction in X4 rlu) are highlighted  
\*Patients 01 and 02 received only 100 mg bid  
na, not available

Figure 1:  
X4 RLU response

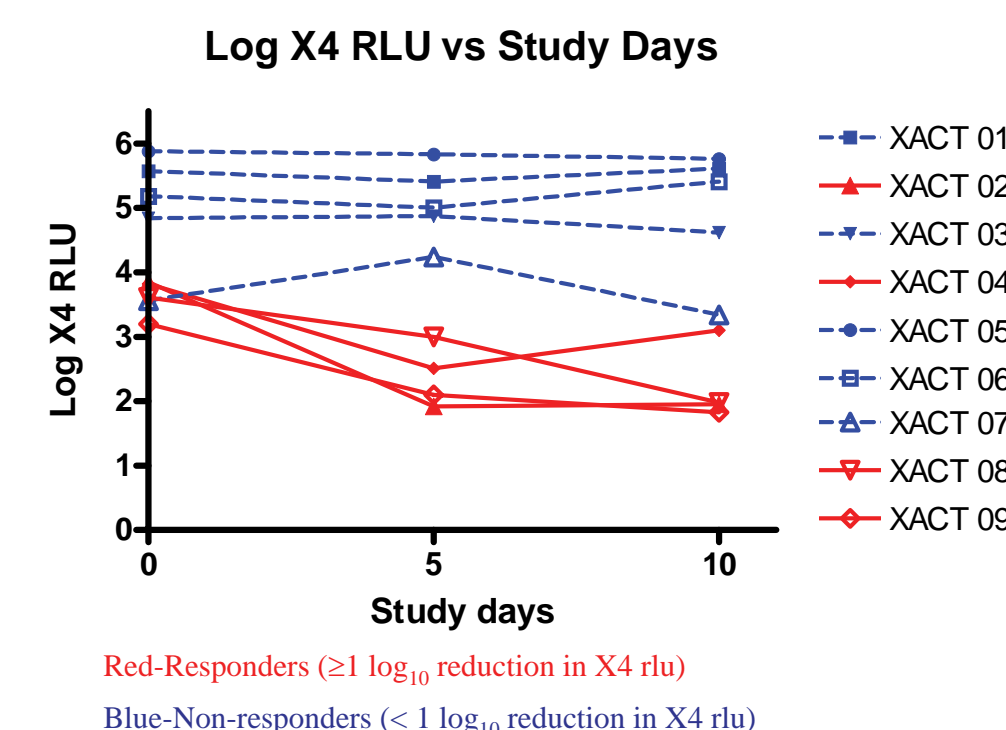


Table 2:  
X4 Virologic Response at 200 mg bid\* (N=9)

X4 RLU Reduction	Day 10	Nadir
1.5 - 2.0 Log <sub>10</sub>	22.2% (2/9)	22.2% (2/9)
1 - 1.5 Log <sub>10</sub>	11.1% (1/9)	22.2% (2/9)
<1 Log <sub>10</sub>	66.7% (6/9)	55.6% (5/9)

\*2 of 9 patients evaluated only received 100 mg bid

Table 3:  
Virologic Response--Tropism

Pt ID	Screening	Tropism			
		0	5	10	17
XACT 01	X4	X4	X4	X4	X4
XACT 02	DM	DM	R5	R5	DM
XACT 03	DM	DM	DM	DM	na
XACT 04	DM	DM	DM	DM	na
XACT 05	DM	X4	DM	DM	X4
XACT 06	DM	DM	DM	DM	DM
XACT 07	DM	na	DM	DM	DM
XACT 08	na	DM	DM	R5	R5
XACT 09	DM	DM	R5	R5	DM

Non-Responders (patients with <1 log<sub>10</sub> reduction in X4 rlu) are highlighted  
Two of the 4 responders harboured DM virus at study entry but showed only R5 virus on Day 5, same change of viral pool was observed in another responder at Day 10.

Table 4:  
Efficacy--others

Pt ID	$\Delta$ X4 RLU	Log HIV RNA		R5 RLU		CD4		WBC	
		Day 0	Day 10	Day 0	Day 10	Day 0	Day 10	Day 0	Day 10
XACT 02	-1.90	4.61	5.08	1.74	1.91	306	228	2.97	2.79
XACT 08	-1.63	4.91	5.86	5.66	6.16	54	99	3.5	3.5
XACT 09	-1.37	4.17	4.50	4.94	5.13	246	219	9.06	6.7
XACT 04	-0.72	5.82	6.58	5.83	5.92	217	310	7.2	10.1
XACT 07	-0.22	5.41	5.83	1.96	5.76	68	56	6.6	10.4
XACT 03	-0.22	4.43	2.92	5.06	5.25	109	271	6.3	7.7
XACT 05	-0.12	6.09	6.38	4.08	4.25	1	4	2.82	2.7
XACT 01	0.04	5.43	5.25	5.88	6.13	129	92	6.76	6.56
XACT 06	0.23	5.1	5.26	4.93	5.18	336	281	7.48	6.7
Median (all)*	-0.22	5.10	5.26	4.94	5.25	129.00	219.00	6.60	6.70
Mean (all)*	-0.66	5.11	5.30	4.45	5.08	162.89	173.33	5.85	6.35
Median (R)*	-1.50	4.76	5.47	5.30	5.53	231.50	223.50	5.35	5.10
Mean (R)*	-1.40	4.88	5.51	4.54	4.78	205.75	214.00	5.68	5.77

Non-Responders (patients with <1 log<sub>10</sub> reduction in X4 rlu) are highlighted

## Conclusion

- 4 of 9 patients achieved  $\geq 1 \log_{10}$  reduction in X4 rlu after 10 days of treatment.
- Responders achieved a median 1.5 log<sub>10</sub> reduction in X4 rlu (Range= -0.72 to -1.90).
- Two of the 4 responders harboured D/M virus at study entry but showed only R5 virus on Day 5, same change of viral pool was observed in another responder at Day 10.
- No significant changes in CD4, CD34, HIV viral load, WBC and R5 rlu were observed.
- AMD11070 was well tolerated at 200 mg twice daily for 10 days. No drug related serious adverse events (AEs) or > grade 2 drug-related AEs were observed. There were no clinically significant abnormal lab values. No hepatotoxicity was observed.

Note:

AMD11070 was recently placed on clinical hold by the FDA due to liver histology changes observed in longer term toxicity experiments. These findings are currently under investigation.

Acknowledgement:  
Thanks to the patients who participated in this study.