Poster # 1062

A phase 1 trial of the combination of 3BNC117 and 10-1074 in HIV-uninfected adults

Yehuda Z. Cohen[1], Allison Butler[1], Rebeka Levin[1], Katrina Millard[1], Maggi Pack[1], Shiraz Belblidia[1], Juan P. Dizon[1], Irina Shimeliovich[1], Kelly E. Seaton[2], Nicole L. Yates[2], Georgia D. Tomaras[2], Marshall Zingg[3], Michael S. Seaman[3], Michel C. Nussenzweig[1,4], Marina Caskey[1]

[1] Laboratory of Molecular Immunology, The Rockefeller University, NY, USA [2]Duke Human Vaccine Institute, Duke University, NC, USA

[3]Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, MA, USA [4]Howard Hughes Medical Institute

BACKGROUND

- Broadly neutralizing anti-HIV-1 antibodies are currently being developed for the treatment and prevention of HIV infection.
- Effective broadly neutralizing antibody therapy or prophylaxis will likely require a combination of antibodies to increase breadth and potency and prevent the emergence of resistance.
- 3BNC117 is a broadly neutralizing CD4-binding site antibody that has been shown to suppress viremia and delay viral rebound.[1,2]
- 10-1074 is a broadly neutralizing antibody that targets the V3-glycan and has also been shown to suppress viremia.[3]
- When administered alone, 3BNC117 was found to have a half-life of approximately 17 days in HIV-uninfected individuals; 10-1074 was found to have a half-life of 24 days in HIV-uninfected individuals.
- Both antibodies have been well tolerated when administered alone.
- This study was performed to evaluate the combination of these 2 antibodies in HIV-uninfected individuals.

STUDY OBJECTIVES

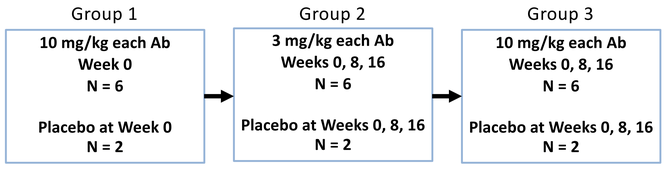
- To evaluate the safety and tolerability of the combination of 3BNC117 and 10-1074 in HIV-uninfected individuals.
- To evaluate the pharmacokinetics of the combination of 3BNC117 and 10-1074 in HIV-uninfected individuals.

STUDY DESIGN

- Placebo-controlled, double blind, randomized trial consisting of 3 groups of 8 participants. The study design is shown in **Figure 1**.
- All participants were enrolled at The Rockefeller University, NY, USA.
- Group 1 received a single dose of both antibodies at 10 mg/kg.
- Groups 2 and 3 received 3 doses of both antibodies 8 weeks apart at 3 mg/kg and 10 mg/kg, respectively.
- Participants in each group were randomized 3:1 to receive the study products or placebo, administered by intravenous infusion.
- Enrollment in each group only began following the availability of 28-day safety data from all participants in the prior group.
- Each antibody was administered over 60 minutes. The second antibody was infused following completion of first infusion.
- Main inclusion criteria: age 18 – 65, behavior consistent with low risk of exposure to HIV.
- Main exclusion criteria: HIV infection, chronic hepatitis B or C, STI within 12 months of enrollment, clinically significant acute or chronic medical condition.

STUDY DESIGN

Figure 1 . Study design



RESULTS

- Twenty-four participants were enrolled. Demographic characteristics for the enrolled participants are shown in **Table 1.**
- All follow up visits have been completed at this time, but the study remains blinded.
- Although the study remains blinded, few adverse events were reported overall. Reactogenicity included 2 instances of headache and 1 of fatigue, all graded as mild, and 1 instance of fever, graded as moderate.
- Additional adverse events considered at least possibly related to the infusions included one instance of elevated bilirubin and a URI.
- Overall, the safety profile of the antibody combination was similar to the safety profile of either antibody administered alone.
- Serum 3BNC117 and 10-1074 levels were measured by anti-idiotype ELISA and compared to results obtained in prior trials of each antibody administered alone **(Figures 2 and 3)**
- Pharmacokinetic analyses have been performed by non-linear mixed effects modeling for Groups 1 and 2.
- The average half-life of 3BNC117 was 18.4 and 15.6 for Group 1 and 2 respectively. **(Table 2)**
- The average half-life of 10-1074 was 22.3 and 20.3 for Group 1 and 2 respectively. **(Table 3)**
- Pharmacokinetic analyses for Group 3 is ongoing.
- Serum neutralizing activity against selected viral strains correlated with measured antibody levels.

Table 1. Demographic characteristics of participants

Category	Subcategory	Group 1	Group 2	Group 3
Gender	Male	8	6	5
	Female	0	2	3
Age (years)	21-30	0	1	4
	31-40	2	2	1
	41-50	3	4	1
	51-60	2	1	2
	61-65	1	0	0
Race	Black	3	6	5
	White	4	0	3
	Multiple/other	1	2	0
Ethnicity	Hispanic	2	2	2

RESULTS

Figure 2. 3BNC117 levels alone and in combination with 10-1074 when administered at 10 mg/kg

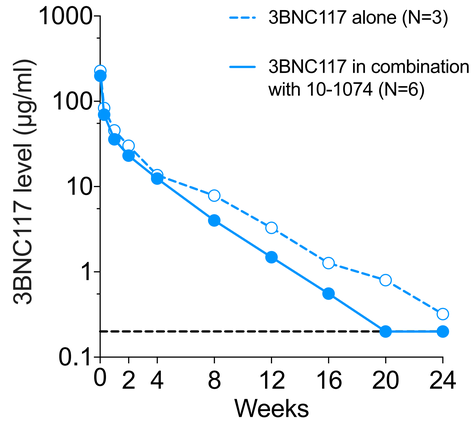


Figure 3. 10-1074 levels alone and in combination with 3BNC117 when administered at 10 mg/kg

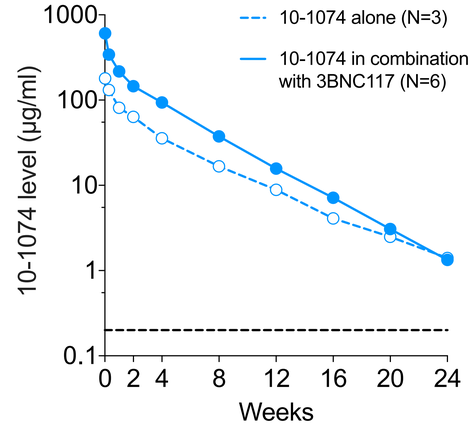


Table 2. Pharmacokinetics of 3BNC117 when administered in combination with 10-1074 (Groups 1 and 2)

Parameter	Group	N	Mean	SD	Min	Max
Clearance (L/day)	1	6	0.58	0.16	0.45	0.85
	2	6	0.63	0.23	0.43	1.08
Half-life (days)	1	6	18.42	2.53	15.92	22.96
	2	6	15.60	6.83	8.26	28.33
AUC (mg*hr/L)	1	6	1216.45	230.31	790.81	1445.33
	2	6	297.35	111.42	193.18	505.35
Cmax (ug/ml)	1	6	270.59	71.13	189.18	362.96
	2	6	68.20	12.21	57.18	86.97

Table 3. Pharmacokinetics of 10-1074 when administered in combination with 3BNC117 (Groups 1 and 2)

Parameter	Group	N	Mean	SD	Min	Max
Clearance (L/day)	1	6	0.11	0.02	0.09	0.13
	2	6	0.11	0.03	0.08	0.18
Half-life (days)	1	6	22.34	1.50	20.75	25.11
	2	6	20.30	2.41	16.02	22.54
AUC (mg*hr/L)	1	6	7132.74	930.01	5794.46	8182.74
	2	6	2084.94	538.12	1526.71	2929.50
Cmax (ug/ml)	1	6	608.75	122.00	458.06	727.43
	2	6	189.00	17.40	158.66	207.76

CONCLUSIONS

- The broadly neutralizing anti-HIV-1 antibodies 3BNC117 and 10-1074 were well tolerated when administered in combination.
- Preliminary pharmacokinetic analyses demonstrate that the half-life of each antibody administered in combination was similar to the half-lives observed for each antibody administered alone.
- These results support the continued development of combinations of broadly neutralizing antibodies for the treatment and prevention of HIV-1 infection.

REFERENCES

1. Caskey M, Klein F, Lorenzi JCC, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. *Nature.* 2015;522:487-491.
2. Scheid JF, Horwitz JA, Bar-On Y, et al. HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. *Nature*. 2016;535: 556–560.
3. Caskey M, Schoofs T, Gruell H, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. *Nat Med*. 2017;23:185-191.

ACKNOWLEDGEMENTS

- We thank all study participants for their contributions to this study.
- This work was supported by the Bill and Melinda Gates Foundation, grant # OPP 1092074.
- Y.Z.C. is supported by grant # KL2TR001865, National Center for Advancing Translational Sciences (NCATS), and grant # UL1 TR000043, NIH Clinical and Translational Science Award (CTSA) program.
- M.C.N. is a Howard Hughes Medical Investigator.