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A Phase 2 Open-Label Trial of Antibody UB-421 Monotherapy as a Substitute for HAART

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BACKGROUND

- UB-421 is a humanized Fc-aglycosylated IgG1 monoclonal antibody (mAb), which binds to conformational epitopes near the CDR2 region on domain-1 of CD4 receptors to block HIV-1 binding and entry into cells (**ref. 1; Figure 1**).
- UB-421 *in vitro* completely neutralized > 850 HIV-1 strains of various sub-genotypes with Clades A-J and with CCR5- or CXCR4-co-receptor usage via a competitive binding (**Figure 2**; tested with its murine prototype B4 at Monogram). UB-421 binds to CD4+ T cells with high affinity (Kd, 5.6 x10^{-11} M), about 100-fold higher than that by gp120 on CD4+ HPB-ALL cells **(Figure 3)**.
- When compared with broadly neutralizing mAbs, including VRC01, 3BNC117, 10-1074 and PGT121, UB-421 exhibited the most potent neutralization activities **(ref. 2)**.
- Its safety and antiretroviral efficacy were previously demonstrated in ART-naïve Asians. In Phase I, a single dose achieved mean maximum (individual nadir) viral load (VL) reduction of 1.6 log10 (2.3 log10). In Phase IIa eight-week repeated-dose trial, mean (±SD) maximum VL reductions of 2.27(±0.6) and 2.45(±0.46) log10 copies/mL were observed for 10mg/Kg/weekly*8 doses and 25mg/Kg/bi-weekly*4 doses, respectively.
- This Phase II trial in ART-stabilized HIV-1(+) adults is to study the safety, tolerability and efficacy of UB-421 monotherapy (NCT02369146).

Figure 1: Functioning sites of various HIV-1 entry inhibitors

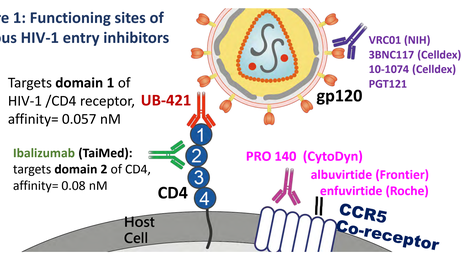
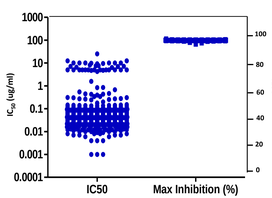
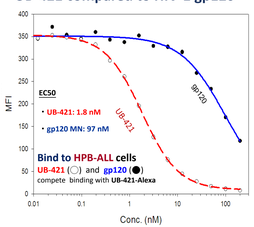


Figure 2. Competitive binding leads to 100% neutralization of >850 HIV isolates



> 850 Env pseudoviruses

Figure 3. Binding affinity (EC50) of UB-421 compared to HIV-1 gp120



METHODS

Subjects: virally-suppressed HIV-1(+) adults on combinational anti-retroviral therapy (cART); in the past year, s/he must have:

a) Used the same cART regimen and no viral rebound;
b) ≧ 2 records of plasma HIV-1 VL < 50 RNA copies/mL
c) ≧ 2 records of CD4+ T cell count ≧ 350 cells/mm^3
d) Not recently used other mAb, investigational drugs, systemic chemotherapy, immunomodulating therapy or vaccines
e) No AIDS-defining illnesses or other active systemic infections

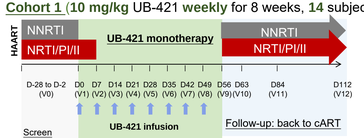
Treatment period: subjects interrupted cART to receive 8 doses of **UB-421 monotherapy** at 10mg/kg weekly or 25mg/kg bi-weekly **(Figure 4)**.

Primary Endpoint: 1) **antiviral efficacy**: cumulative percentages of and time to viral rebound, which was defined as plasma VL ≧ 400 copies/mL for two consecutive visits during UB-421 monotherapy period; 2) **tolerability** and **safety** of 8 doses of UB-421 regimen.

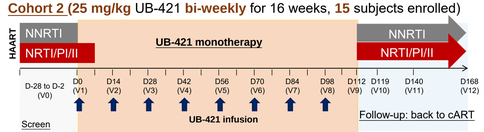
Re-initiation of cART, if any of the following occurred: 1) viral rebound, 2) any HIV-related symptoms, 3) complete, discontinue or withdrew UB-421 therapy. After cART re-initiation, subjects were followed for at least 8 weeks or until VL stably below 50 copies/mL.

Figure 4: Two regimen schedules of UB-421 substitution therapy

Cohort 1 (10 mg/kg UB-421 weekly for 8 weeks, 14 subjects enrolled)



Cohort 2 (25 mg/kg UB-421 bi-weekly for 16 weeks, 15 subjects enrolled)



RESULTS

Subjects: of 36 Asians screened, 29 males meeting all criteria were allocated to 2 cohorts (**Table 1**); 27 completed all 8 doses of UB-421.

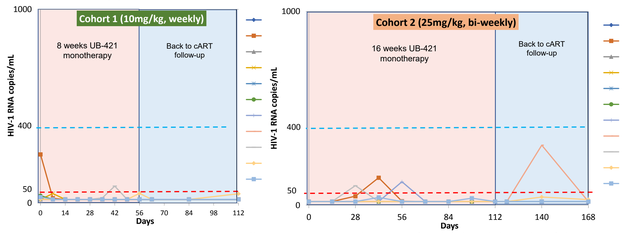
Table 1: Baseline characteristics of the enrolled (median (range)

	Cohort 1 10 mg/kg weekly	Cohort 2 25 mg/kg bi-weekly
Age (year)	35 (25 – 47)	30.5 (21 – 56)
Weight (Kg)	70.3 (55 – 97.1)	62.3 (45.5 – 73.8)
Year of HIV infection	5.65 (2.9 – 17.7)	5.75 (1.3 – 15.7)
CD4+ T cell counts/ mm^3	653 (370 – 951)	641 (416 – 1087)
CD8+ T cell counts/ mm^3	721 (392 – 1145)	718 (379 – 1511)

RESULTS

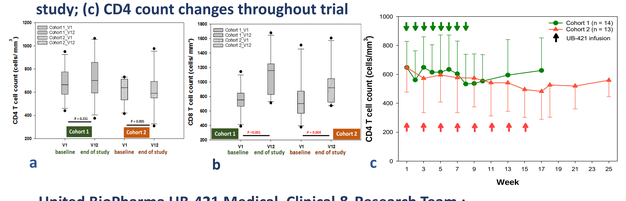
- Of 29 enrolled, 1 lost to follow-up and 1 withdrew due to grade-2 skin rash in cohort 2. **Tolerability** is **100%** (14/14) for cohort 1 and **93%** (14/15) for cohort 2.
- 22 of the 27 completers re-started the scheduled cART after UB-421 monotherapy; **no viral rebound** was detected in **both treatment and follow-up periods (Figure 5)**. Single episode of viral blip (VL= 50-400) was detected in 3 and 4 subjects in cohorts 1 and 2, respectively. **VLs were all < 50 copies/mL** at the end of 8-week follow-up.
- 3 and 2 subjects in cohorts 1 and 2, respectively refused to resume cART at the scheduled time and signed consents; their **VLs were all < 50 copies/mL** during the UB-421 treatment period. In the follow-up, viral rebound was detected **35-62 days** after the last dose of UB-421. All 5 subjects re-started cART right after the rebound, and were monitored for reaching stable viral suppressions.

Figure 5. HIV-1 viral load change over time for subjects who finished UB-421 monotherapy and re-initiated cART at scheduled time: no viral rebound



- Each subjects' CD4 and CD8 cell percentages and counts (and other lab. values) by standard hospital diagnostics were compared as pairs between baseline, the ends of treatment and of study by Wilcoxon signed rank test
- **CD4+ cell counts remained stable** after the UB-421 monotherapy for both cohort 1 (p=0.33) and cohort 2 (p=0.91; boxplots **Figure 6a**)
- **CD8+ cell counts increased significantly** after 8 doses of UB-421 therapy for both cohort 1 (p<0.001) and cohort 2 (p=0.004; **Figure 6b**)
- An anti-CD4 domain 2 antibody was used to monitor CD4 count changes at each study visit and **no substantial changes** were observed for both cohorts (**Figure 6c**)

Figure 6. (a) CD4+ cell and (b) CD8+ cell counts before treatment and at end of study; (c) CD4 count changes throughout trial



United BioPharma UB-421 Medical, Clinical & Research Team :

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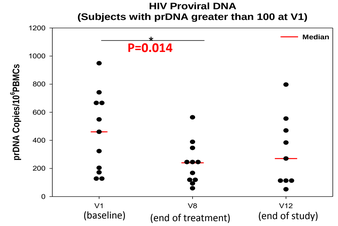
RESULTS

- PBMCs were quantified for **HIV proviral DNA** (prDNA; including circular, integrated, pre- and un-integrated) using primers targeted at HIV-1 Gag p24.
- Among 11 subjects with prDNA > 100 copies/ 10^6 PBMC at baseline (V1), 10 showed a mean **2.24-fold reduction** at the end of treatment (V8, p=0.014, Wilcoxon signed rank test; **Figure 7).**
- HIV-1 reservoir, as surrogated by prDNA levels, was markedly reduced during UB-421 monotherapy, implying that UB-421 has a great potential for the functional cure of HIV-1 infections.

Figure 7. HIV proviral DNA at baseline, end of treatment and end of study



- Of all possible or probable drug-related adverse events (AEs), the most common was grade-1 or grade-2 **skin rash** in 48.3% of the 29 subjects.
- No death or drug-related severe AEs occurred till the end of follow-up. Overall, **UB-421 was safe and well tolerated** (Table 2).

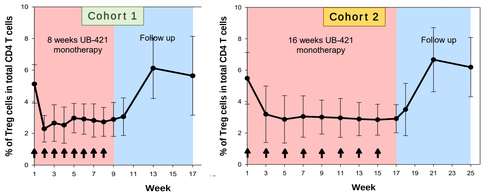
Table 2. AEs or laboratory abnormalities of grade 2 or above developed during the trial period

	Cohort 1	Cohort 2
	No. of subjects (%)	
Skin rash	1 (7.1%)	2 (13.3%)
Eosinophilia	1 (7.1%)	2 (13.3%)
ALP elevation	1 (7.1%) [a]	0
Bilirubin elevation		0
ALT elevation		1 (6.7%)
AST elevation		2 (13.3%)

a. All liver enzyme elevations were from a single subject who, at onset, were tested negative for all viral hepatitis. He had been consuming green tea extract and herbal supplements before the onset, which occurred at the last dose of UB-421. The elevations were all normalized 2-3 weeks after stopping the supplements without any specific treatments for the hepatitis.

- Percentages of **CD4+ T regulatory** cells **significantly reduced** (interquartile range = 1.7–3.1) **during UB-421 monotherapy** for both cohorts (end of treatment p<0.01 by Wilcoxon signed-rank test; **Figure 8**)
- Other studies had shown: removal of Tregs increases HIV-specific T-cell responses, and HIV patients with low Tregs have higher immune activation.

Figure 8. Changes of CD25+FoxP3+ % on CD4+ lymphocytes during trial



CONCLUSIONS

- **All subjects who underwent cART interruption and received UB-421 monotherapy showed no viral rebound (100% success rate) during the 8- or 16- weeks treatment period.**
- **Both 10 mg/kg weekly (Cohort 1) and 25 mg/kg bi-weekly (Cohort 2) regimens were similarly effective in suppressing viremia.**
- **UB-421 monotherapy was safe and well tolerated. The overall tolerability of this phase II trial was 96.55%.**
- **No anti-UB-421 antibodies were detected in any of the 29 subjects during the treatment and follow-up periods.**
- **Subjects' CD4 T cell counts remained stable before and after the study, while CD8 T cell counts increased.**
- **All subjects' Treg percentages significantly reduced during the treatment period, suggesting an enhancement of host immunity by UB-421. After completion of UB-421 treatment, Treg % returned to baseline levels.**
- **For subjects with high HIV proviral DNA (prDNA) before trial, prDNA decreased significantly after UB-421 treatment, and such reduction still maintained during the follow-up. This suggests that UB-421 can reduce HIV viral reservoir and may help achieving the goal of functional cure.**
- **UB-421 warrants further evaluation for an indication as a monotherapy for ART substitution in HIV-1 suppressed adults.**

References

1. Designed deimmunized monoclonal antibodies for protection against HIV exposure and treatment of HIV infection. Lynn, S and Wang, CY. 2009, U.S. Patent No. 7,501,494B2.
2. Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption. Bar KJ, Sneller MC, Harrison LJ, … , Fauci AS, Tebas P, Chun TW. **N Engl J Med. 2016** Nov 24;375(21):2037-2050.