A Phase 2 Open-Label Trial of Antibody UB42-Monotherapy as a Substrate for HAART

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BACKGROUND

• UB-42 is a humanized IgG1-κ Fab-fragmentated mAb monochlonal antibody (mAb), which binds to conformational epitopes near the C2 region on gp120, the viral envelope glycoprotein, to block HIV-1 binding and entry into cells (ref. 1, figure 1).

• UB-42 in vivo completely neutralized 850 HIV-1 strains of various viral subtypes from Patients and ADLs and cross-reacted with gp120-CD4 due to its broad and tight epitope coverage, which made it an ideal mAb for testing in the preclinical studies (figure 2). It is well-tolerated in the chronic phase of HIV-1 infection and shows good safety and testability in SSACT trial (ref. 2).

• So safety and antiretroviral efficacy were previously demonstrated in ART-naive Asians. In Phase 1, a single dose achieved mean maximum (individual early) viral load (VL) reduction of 1.6 log10 (2.2 fold). In Phase 1a eight repeated-dose trial, mean (median) maximum VL reductions of 2.3 (1.7) fold and (0.55-2.45) log10 copies/mL were observed for 10 mg/kg weekly for 8 weeks and 25 mg/kg twice weekly for 4 weeks, respectively. 3 This Phase 2 trial in ART-stabilized HIV-1(a) adults is to study the safety, tolerability and antiretroviral efficacy of UB-42 monotherapy (NCT03364510).

METHODS

• Subjects: virologically-suppressed (VR-S) adults on combination antiretroviral therapy (ART): in the past year, n=100

• ART: (a) were on stable ART for ≥12 months prior to randomization and had baseline VL <50 RNA copies/mL

• UB-42 was administered at 400 mg/kg biweekly

• Primary Endpoint: antiretroviral efficacy: cumulative percentages of and ART-resistant mutations, which was defined as plasma viral RNA >850 copies/mL for two consecutive visits during UB-42 monotherapy period: tolerability and safety of 6-8 doses of UB-42 regimen

• Re-initiation of ART: if any of the following occurred: viral rebound, 1 x viral load ≥1000 copies/mL, CD4 cell count ≤500 copies/mL, observed for 10 mg/kg weekly for 8 weeks and 25 mg/kg twice weekly for 4 weeks, respectively.

RESULTS

1. UB-42 neutralized >850 HIV isolates

2. UB-42 neutralized HIV strains in vitro and in vivo

3. UB-42 neutralized strains from and across viral subtypes

4. No 6000 killing or other acute systemic infections

5. Subjects entered trial on ART (cART) and were treated with UB-42 monotherapy at 100 mg/kg weekly for 25 mg/kg biweekly (figure 4).

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• The Phase 2 trial in ART-stabilized HIV-1(a) adults is to study the safety, tolerability, and antiretroviral efficacy of UB-42 monotherapy (NCT03364510).

Each subjects’ CD4 and CD8 cell counts and counts and (and other lab values) by standard laboratory tests and were assessed at baseline and at week 24 of UB-42 monotherapy treatment for each subject.

CD4+ T cell counts remained stable after the UB-42 monotherapy for both cohort 1 and cohort 2 patients (figure 6).

CD4+ T cell counts increased significantly after UB-42 monotherapy for both cohort 1 and cohort 2 patients (figure 6).

CD8+ T cell counts significantly increased after UB-42 monotherapy for both cohort 1 and cohort 2 patients (figure 6).

An anti-HIV-2 domain 2 antibody was used to monitor CD4 counts changes at each study visit and no substantial changes were observed for both cohorts (figure 6).

A change in CD4 count was observed before treatment and at end of study (CD4 count changes throughout trial

• Of possible or probable drug-related adverse events (ref. 4), the most common was grade-1 or grade-2 skin (100%)

• No death or drug-related severe AEs occurred until the end of the study period, Overall, UB-42 was safe and well tolerated (Table 2).

Table 2. AEs or laboratory abnormalities of grade 2 or above developed during UB-42 monotherapy

• UB-42 monotherapy was safe and well tolerated. The overall tolerability of this phase II trial was 96.15%

• No severe or unexpected AEs were detected in any of the subjects during the treatment and follow-up periods.

• Subjects’ CD4 cell counts remained stable before and after the study, while CD8 cell counts increased.

• Subjects’ Treg percentages significantly decreased during the treatment period, suggesting the improvement of host immune response after UB-42 completion of UB-42 treatment, Treg % returned to baseline levels.

• For subjects with high HIV proviral DNA (pDNA) before trial, pDNA decreased 18 - 39% after UB-42 monotherapy, and such a level was maintained during the follow-up. This suggests that UB-42 reduce HIV viral burden and may help achieve viral suppression. Preliminary data from UB-42 suggests that UB-42 warrants further evaluation for an indication as a monotherapy in HIV suppression in HAART-suppressed adults.

CONCLUSIONS

1. All subjects who underwent cART interruption and received UB-42 monotherapy showed no viral rebound (100% success rate) during the 8–12 weeks treatment period.

2. Both 10 mg/kg biweekly ( Cohort 1) and 25 mg/kg biweekly (Cohort 2) regimens were effectively in anti-viral activity.

3. UB-42 monotherapy was safe and well tolerated. The overall tolerability of this phase II trial was 96.15%.

4. No severe or unexpected AEs were detected in any of the subjects during the treatment and follow-up periods.

5. Subjects’ CD4 cell counts remained stable before and after the study, while CD8 cell counts increased.

6. Subjects’ Treg percentages significantly decreased during the treatment period, suggesting the improvement of host immune response after UB-42 completion of UB-42 treatment, Treg % returned to baseline levels.

7. For subjects with high HIV proviral DNA (pDNA) before trial, pDNA decreased 18 - 39% after UB-42 monotherapy, and such a level was maintained during the follow-up. This suggests that UB-42 reduce HIV viral burden and may help achieve viral suppression. Preliminary data from UB-42 suggests that UB-42 warrants further evaluation for an indication as a monotherapy in HIV suppression in HAART-suppressed adults.

8. UB-42 monotherapy significantly reduced (intrapeptide range of 17–11) during UB-42 monotherapy for both cohorts (level of treatment p<0.01 by Wilcoxon signed rank test). Figure 9

9. Other studies has shown: remission of lupus, hepatitis, specific T cell responses, and HIV patients with low Tregs have higher immune activation.

References


3. Data on File. Wai Wong, MD

4. Data on File. Wen Su, Hsu


7. Data on File. Wai Wong, MD

8. Data on File. Wen Su, Hsu