Immune Biomarker Characterisation of Amtabafusp (ABF), a Bispecific T-Cell Engager, in a Phase 1b Study of People With HIV

WEPEB128

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Conclusions

- In virologically suppressed people with HIV, administration of amtabafusp alfa was associated with a coordinated immune response, including cytokine induction, as well as $CD4^+$ and $CD8^+$ T-cell engagement, redistribution, activation, and proliferation
- T cell–related cytokines initially increased in a dose-dependent manner and plateaued at higher exposures, whereas proinflammatory and regulatory cytokines continued to increase with escalating doses
- HIV-1 proviral DNA levels did not significantly change after amtabafusp alfa monotherapy, suggesting combination regimens may be necessary to impact the latent HIV-1 reservoir
- Amtabafusp alfa administration was associated with pharmacodynamic changes consistent with the mechanism of action of bispecific T-cell engagers
- Overall, these findings highlight the potential value of combining amtabafusp alfa with latency-reversal strategies to enhance target engagement and enable measurable impact on the latent HIV reservoir

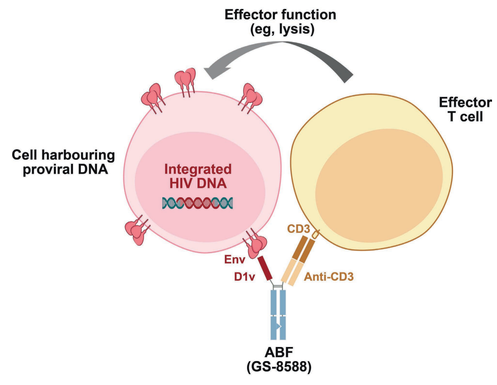
Plain Language Summary

- Antiretroviral therapy is a type of medicine that treats HIV and helps stop the virus from spreading
  - However, if people with HIV stop taking this therapy, the virus can return; this happens because some HIV hides in cells in the body where the medicine cannot reach
- Amtabafusp alfa is being studied as a new type of medicine that helps the immune system find and kill cells with HIV, including those that hide from antiretroviral therapy
  - Researchers are studying this medicine as part of a combination of drugs that might help cure HIV
- This study showed that amtabafusp alfa made the immune system more active; however, it did not reduce the amount of hidden HIV in the body
- More studies are needed to understand whether amtabafusp alfa can be combined with other drugs to help cure HIV

Introduction

- The persistence of a latent viral reservoir represents a key barrier to achieving an HIV cure[1]
- Bispecific T-cell engagers have the potential to redirect cytotoxic T cells to cells harbouring HIV, targeting them for elimination[2,3]
- Amtabafusp alfa (ABF; GS-8588) is a novel HIV bispecific T-cell engager consisting of an envelope (Env)-targeting engineered CD4 domain 1 variant paired with an anti-CD3 T cell–engaging antigen-binding fragment (**Figure 1**)
  - In vitro, ABF facilitates potent, broad, and specific killing of $CD4^+$ T cells harbouring a diverse panel of HIV clinical isolates[4]
  - ABF demonstrated no adverse findings in nonhuman primate models[4,5] and was generally safe and well tolerated in a Phase 1b study of virologically suppressed (VS) people with HIV (PWH)[6,7]
  - In VS PWH, median CD3 receptor occupancy (CD3RO) in $CD2^+$ T cells increased proportionally to dose and peaked at 70%, 83%, and 91% 2 hours after administration of ABF 30 mg, 75 mg, and 150 mg, respectively, indicating T-cell engagement; no CD3RO accumulation was observed after multiple dosing[6,7]

Figure 1. ABF Mechanism of Action



ABF, amtabafusp alfa; D1v, domain 1 variant; Env, envelope.

For CD3RO in the Phase 1b study of VS PWH, please scan the QR code

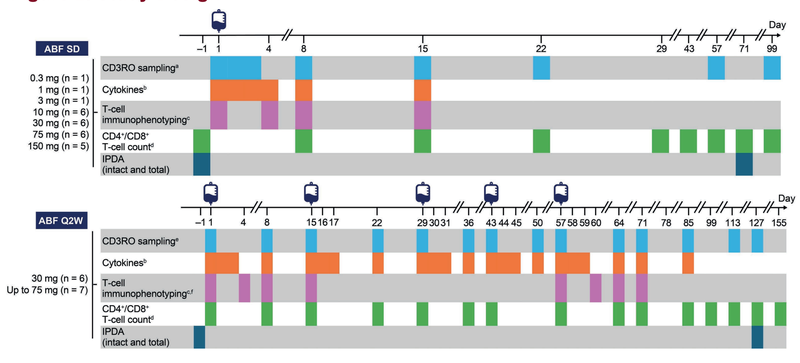
Objective

- To evaluate the effect of ABF administration on immune biomarkers and the HIV-1 reservoir in VS PWH

Methods

- A randomised, blinded, placebo-controlled, Phase 1b study was conducted in VS PWH aged ≥18 years on stable antiretroviral therapy (**Figure 2**)
- Participants were randomised to receive intravenous infusions of ABF or placebo in single ascending doses (SAD; 0.3-150 mg) or multiple ascending doses (MAD; 30 mg at first dose, followed by 30 mg or 75 mg every 2 weeks for 5 doses total)
- At prespecified time points, CD3RO, absolute $CD4^+$ and $CD8^+$ T-cell counts, and markers of T-cell activation (CD69) and proliferation (Ki-67) were assessed by flow cytometry; serum cytokines were measured using Meso Scale Discovery V-PLEX assays
- The latent viral reservoir was measured using the intact proviral DNA assay (Accelevir)

Figure 2. Study Design



Study design

Randomised, blinded, placebo-controlled, Phase 1b study

Key eligibility criteria:

- Aged ≥18 y
- Plasma HIV-1 RNA <50 copies/mL
- VS on stable antiretroviral for ≥6 mo
- $CD4^+$ cell count ≥350 cells/μL

[a]For the SAD cohort, CD3RO samples were collected on Day 1 at predose and multiple time points up to 48 hours post dose and at any time during all other clinical visits where CD3RO samples were collected.
[b]The cytokine serum sampling schedule was subject to alteration based on emerging data. Cytokine serum sampling was conducted predose, at the end of the infusion, and at 4 hours post dose on dosing days, in addition to the other time points indicated.
[c]Samples of whole blood for T-cell responses were collected predose on dosing days.
[d]$CD4^+/CD8^+$ T-cell count sampling was conducted predose on dosing days.
[e]For the ABF 30 mg group within the MAD cohort, CD3RO samples were collected on Day 1 at predose and at 2 hours post dose; on Days 15, 29, and 43 at predose; and at any time during all other clinical visits where CD3RO samples were collected. For the ABF up to 75 mg group within the MAD cohort, CD3RO samples were collected on Days 1, 15, 29, 43, and 57 at predose and at 2 hours post dose and at any time during all other clinical visits where CD3RO samples were collected.
[f]Samples of whole blood for T-cell responses were collected at additional time points not shown.
ABF, amtabafusp alfa; CD3RO, CD3 receptor occupancy; IPDA, intact proviral DNA assay; MAD, multiple ascending dose; Q2W, every 2 weeks; SAD, single ascending dose; SD, single dose; VS, virologically suppressed.

Results

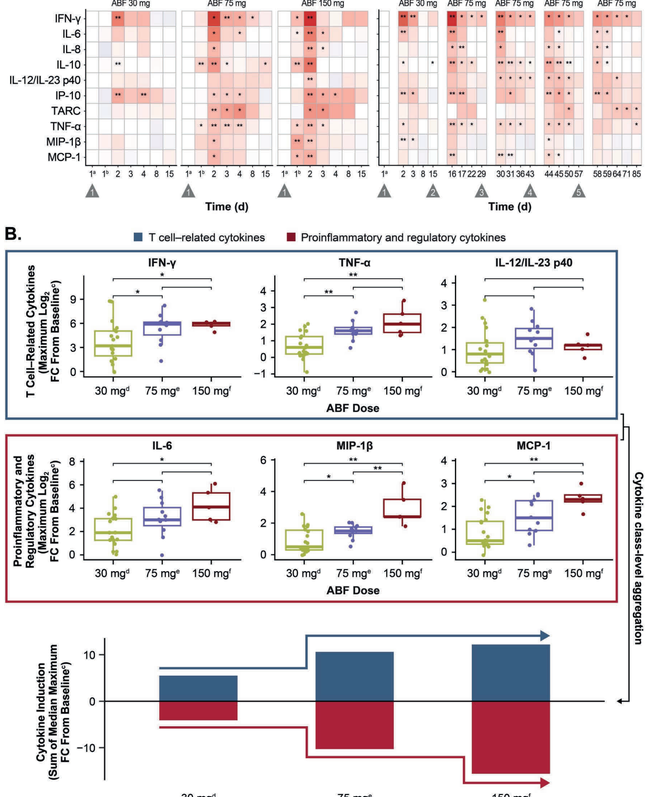
Study Participants

- A total of 54 participants (SAD, n = 37; MAD, n = 17) were randomised and received ≥1 dose of study drug
  - Of these, 39 participants (SAD, n = 26; MAD, n = 13) received ABF and 15 participants (SAD, n = 11; MAD, n = 4) received placebo

Cytokine Responses

- In both SAD and MAD cohorts, dose-dependent cytokine responses were observed with peak induction approximately 24 hours post dose (**Figure 3A**)
  - T cell–related cytokines increased in a dose-dependent manner, but they plateaued at higher ABF doses (**Figure 3B**)
  - Proinflammatory and regulatory cytokines increased with ABF dose and did not plateau within the evaluated dose range

Figure 3. (A) Cytokine Responses Following SAD and MAD of ABF and (B) Differential Dose-Response Profiles of T Cell–Related and Proinflammatory and Regulatory Cytokines Following ABF Administration in SAD and MAD Cohorts

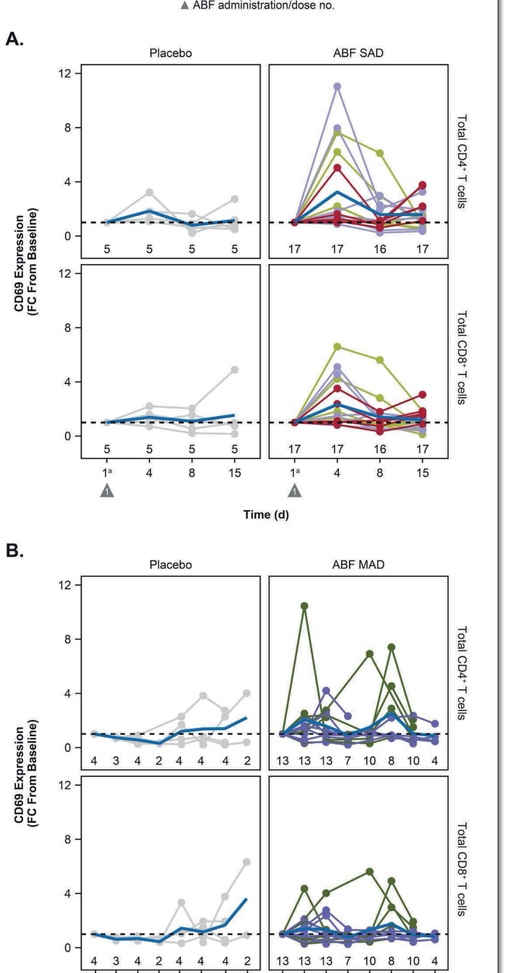


[a]Sample taken predose.
[b]Sample taken 4 hours post dose.
[c]Maximum (peak) FC cytokine response was defined as the highest baseline-normalised postdose value across all time points for each participant.
[d]Combined ABF 30 mg SAD and ABF 30 mg MAD cohorts.
[e]Combined ABF 75 mg SAD and ABF up to 75 mg MAD cohorts.
[f]ABF 150 mg SAD cohort.
*P <0.05. **P <0.01. Statistical comparisons were performed using the Wilcoxon rank sum test.
ABF, amtabafusp alfa; FC, fold change; IFN-γ, interferon gamma; IL, interleukin; IP-10, IFN-γ–induced protein-10; MAD, multiple ascending dose; MCP-1, monocyte chemoattractant protein-1; MIP, macrophage inflammatory protein-1 beta; p40, subunit beta of IL-12/IL-23; SAD, single ascending dose; TARC, thymus- and activation-regulated chemokine; TNF-α, tumour necrosis factor alpha.

T-Cell Immunophenotyping and Counts

- CD69 expression, a marker of T-cell activation, increased on both $CD4^+$ and $CD8^+$ T cells following ABF administration, with peak expression observed on Day 4 (**Figure 4**)
- Repeated increases in CD69 expression were observed in participants who received multiple ABF 30 mg doses; these increases were not observed after higher multiple-dose administrations

Figure 4. $CD4^+$ and $CD8^+$ T-Cell Activation by CD69 Expression Following (A) SAD and (B) MAD ABF Administration

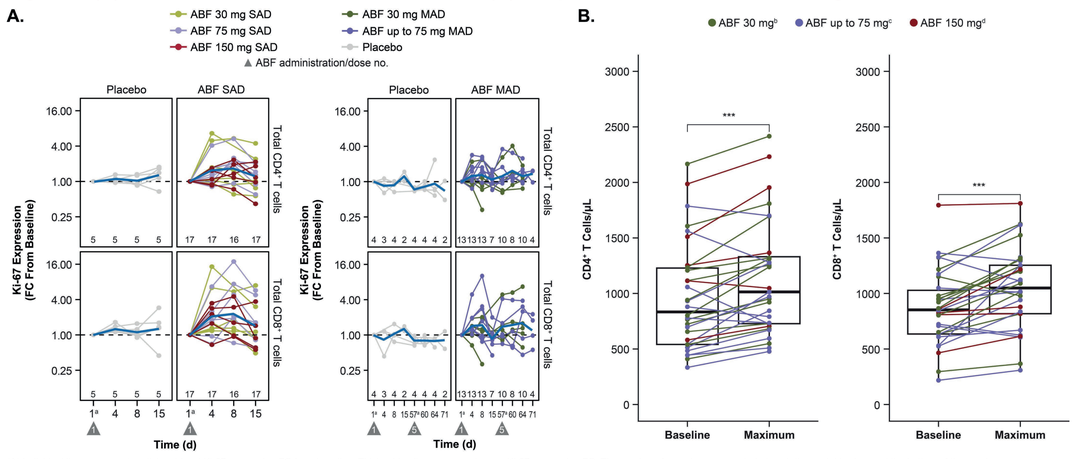


Individual lines represent participant-level CD69 expression FC from baseline. Thicker blue lines represent mean CD69 expression FC. The number of samples represented at each time point is shown at the bottom of the graph.
[a]Sample taken predose.
ABF, amtabafusp alfa; FC, fold change; MAD, multiple ascending dose; SAD, single ascending dose.

Pharmacodynamic Changes

- Ki-67 expression, a marker of T-cell proliferation, increased on both $CD4^+$ and $CD8^+$ T cells following ABF administration, with peak expression observed between Days 4 and 8 (**Figure 5A**)
- Consistent with increases in Ki-67 expression, peripheral $CD4^+$ and $CD8^+$ T-cell counts increased following ABF administration in both SAD and MAD cohorts (**Figure 5B**)

Figure 5. (A) $CD4^+$ and $CD8^+$ T-Cell Proliferation and (B) Peripheral T-Cell Counts Following ABF Administration



(A) Individual lines represent participant-level Ki-67 expression FC from baseline. Thicker blue lines represent mean Ki-67 expression FC. The number of samples represented at each time point is shown at the bottom of the graph.
(B) Box plots represent median (IQR) peripheral T-cell counts. Statistical comparisons were performed using the Wilcoxon signed rank test. SAD and MAD cohorts are combined (n = 30). Maximum (peak) peripheral T-cell count was defined as the highest observed postdose value across all time points for each participant.
[a]Sample taken predose.
[b]Combined ABF 30 mg SAD and ABF 30 mg MAD cohorts.
[c]Combined ABF 75 mg SAD and ABF up to 75 mg MAD cohorts.
[d]ABF 150 mg SAD cohort.
***P <0.001.
ABF, amtabafusp alfa; FC, fold change; MAD, multiple ascending dose; SAD, single ascending dose.

Latent HIV-1 Reservoir

- The fold changes from baseline for both intact and total proviral HIV-1 DNA were not significantly different between ABF and placebo cohorts (**Figure 6**)

Figure 6. Change From Baseline in Intact and Total Proviral HIV-1 DNA

Each point represents participant-level FC in intact or total proviral HIV-1 DNA from baseline. Median (IQR) values are highlighted in blue. Comparison was limited to participants receiving ABF 10 mg to 150 mg SAD or ABF 30 mg up to 75 mg MAD. The number of samples represented in each treatment group is shown at the bottom of the graph. Statistical comparisons were performed using the Wilcoxon rank sum test; differences between the ABF and placebo cohorts were not statistically significant.
ABF, amtabafusp alfa; FC, fold change; MAD, multiple ascending dose; SAD, single ascending dose.

Limitation

- The current study is limited by its relatively small sample size; larger studies are needed to more robustly characterise the changes in immune biomarkers associated with ABF administration

References: 1. Chun TW, et al. *Nat Immunol*. 2015;16:584-9. **2.** Brozy J, et al. *J Virol*. 2018;92:e00491-18. **3.** Yang H, et al. *Front Immunol*. 2018;9:2861. **4.** Lam CYK, et al. Presented at: AIDS 2024, the 25th International AIDS Conference; 22-26 July 2024; Munich, Germany. Abstract code WEPEA019. **5.** Selzer L, et al. Presented at: West Coast Retrovirus Meeting; 3-5 October 2024; Palm Springs, CA, USA. **6.** Workowski K, et al. Presented at: Keystone Symposia; 16-19 April 2026; Breckenridge, CO, USA. Poster 2022. **7.** Workowski K, et al. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 22-25 February 2026; Denver, CO, USA. Poster 371.

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