Safety, Pharmacokinetics, and Pharmacodynamics of Amtabafusp, a Bispecific T-Cell Engager, in People With HIV

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Conclusions

- Amtabafusp alfa was generally safe in people with HIV who were virologically suppressed, with manageable cytokine release syndrome and mild-to-moderate reversible dermatologic adverse events
- Amtabafusp alfa demonstrated linear pharmacokinetics from 10 to 150 mg
- T-cell engagement was demonstrated through dose-dependent CD3 receptor occupancy, consistent with the mechanism of action of amtabafusp alfa
- Analyses are ongoing to evaluate immune activation and its effect on the HIV reservoir to elucidate the mechanism of action of amtabafusp alfa and inform on the risk-benefit profile of bispecific T-cell engagers for an HIV cure

Plain Language Summary

- Antiretroviral therapy is effective in treating HIV symptoms and reducing its spread
  - However, if people with HIV stop taking their antiretroviral therapy, the virus usually comes back because some cells with HIV hide in the body where antiretroviral therapy cannot reach them
- Amtabafusp alfa is a new type of medicine, similar to an antibody, made to help the body's immune system find and kill cells with HIV
  - This drug could be an important part of a combination of medicines that might one day lead to an HIV cure
- This study found that amtabafusp alfa is safe for people with HIV and works with the body's immune cells as expected
- More studies are needed to understand the risks and benefits of amtabafusp alfa as a potential component of a cure for HIV

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: International AIDS Conference; July 22-26, 2024; Munich, Germany. Abstract code WEPEA019. **5.** Selzer L, et al. Presented at: West Coast Retrovirus Meeting; October 3-5, 2024; Palm Springs, CA, USA. **6.** O'Brien N, et al. *MAbs*. 2025;17:2440578.

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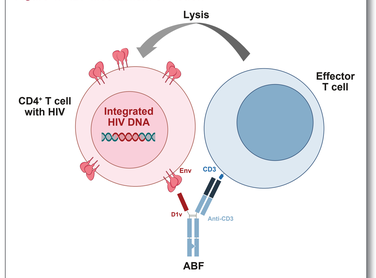
Introduction

- Eradication of the latent reservoir is a key objective for an HIV cure[1]
- Bispecific T-cell engagers offer a promising approach by redirecting cytotoxic T cells to eliminate cells harboring HIV[2,3]
- Amtabafusp alfa (ABF; GS-8588) is a novel bispecific T-cell engager consisting of an Env-targeting engineered CD4 domain 1 variant paired with an anti-CD3 T-cell engaging antigen-binding fragment (**Figure 1**), which enables T-cell activation and redirection against cells with HIV
  - ABF mediates potent, broad, and specific killing of $CD4^+$ T cells infected with a diverse panel of HIV clinical isolates in vitro[4]
  - ABF demonstrated no adverse findings in nonhuman primate studies[4,5]
  - In a simian immunodeficiency virus rhesus macaque model, ABF reached nearly 100% CD3 receptor occupancy 30 minutes after administration
  - ABF also demonstrated similar viral rebound kinetics and viral setpoint to placebo after an analytical treatment interruption, though repeated dosing triggered antidrug antibodies that reduced exposure; despite variable outcomes, higher ABF exposure correlated with greater reduction in viral setpoint after treatment interruption, supporting further evaluation of ABF in HIV cure strategies[5]
  - ABF is currently under investigation as a component of a combination regimen for an HIV cure

Figure 1. ABF Mechanism of Action



ABF, amtabafusp alfa; D1v, domain 1 variant.

Objective

- To evaluate the safety, pharmacokinetics, and pharmacodynamics of ABF in people with HIV (PWH) who were virologically suppressed

Methods

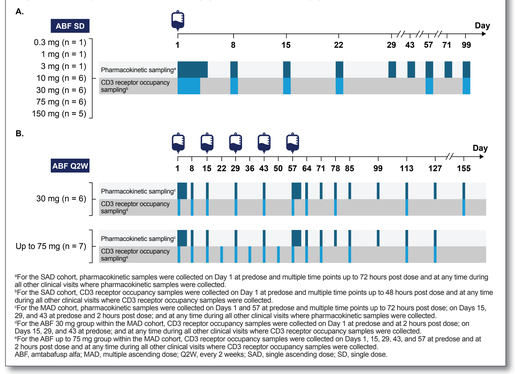
Study Design

- A randomized, blinded, placebo-controlled, Phase 1 study was conducted
  - Eligible participants included adults ≥18 years of age with plasma HIV-1 RNA <50 copies/mL at screening who were on stable antiretroviral therapy for ≥6 months prior to screening and throughout the duration of study treatment and follow-up
  - Eligible participants had no documented history of clinically significant resistance to the current antiretroviral regimen, $CD4^+$ cell count ≥350 cells/μL, and no documented pre–antiretroviral therapy $CD4^+$ nadir <100 cells/μL
- PWH were randomized to receive intravenously administered ABF or placebo in single ascending doses (SADs; 0.3-150 mg) or multiple ascending doses (MADs; 30 mg at the first dose followed by 30 or 75 mg every 2 weeks [Q2W] for 5 doses in total; **Figure 2**)

End Points

- The safety of ABF was evaluated by the incidence of treatment-emergent adverse events (TEAEs)
- Serum pharmacokinetic parameters of ABF were evaluated for up to 99 days after dosing for the SAD cohort and for up to 155 days after the first dose for the MAD cohort
- CD3 receptor occupancy was assessed in whole blood samples using flow cytometry to evaluate the pharmacodynamics of ABF

Figure 2. Study Procedures in the (A) SAD Cohort and (B) MAD Cohort



[a]For the SAD cohort, pharmacokinetic samples were collected on Day 1 at predose and multiple time points up to 72 hours post dose and at any time during all other clinical visits where pharmacokinetic samples were collected.
[b]For the SAD cohort, CD3 receptor occupancy 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 CD3 receptor occupancy samples were collected.
[c]For the MAD cohort, pharmacokinetic samples were collected on Days 1 and 57 at predose and multiple time points up to 72 hours post dose; on Days 15, 29, and 43 at predose and 2 hours post dose; and at any time during all other clinical visits where pharmacokinetic samples were collected.
[d]For the ABF 30 mg group within the MAD cohort, CD3 receptor occupancy 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 CD3 receptor occupancy samples were collected.
[e]For the ABF up to 75 mg group within the MAD cohort, CD3 receptor occupancy 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 CD3 receptor occupancy samples were collected.
ABF, amtabafusp alfa; MAD, multiple ascending dose; Q2W, every 2 weeks; SAD, single ascending dose; SD, single dose.

Results

Study Participants

- Overall, 54 participants were randomized and received ≥1 dose of study drug (SAD cohort, n = 37; MAD cohort, n = 17)
  - **Table 1** summarizes the demographic and baseline characteristics of the SAD and MAD cohorts

Table 1. Demographic and Baseline Characteristics

	SAD Cohort		MAD Cohort	
	ABF (n = 26)	Placebo (n = 11)	ABF (n = 13)	Placebo (n = 4)
Age, y, median (range)	37 (27-75)	59 (27-71)	49 (30-69)	47 (32-57)
Sex at birth, male, n (%)	22 (85)	10 (91)	8 (62)	3 (75)
Race, n (%)				
Asian	0	0	0	1 (25)
Black or African American	15 (58)	6 (55)	5 (38)	2 (50)
White	10 (38)	4 (36)	7 (54)	1 (25)
Other	1 (4)	1 (9)	1 (8)	0
Ethnicity, Hispanic or Latino, n (%)	6 (23)	2 (18)	2 (15)	0
Body mass index, kg/m², mean (SD)	27.5 (3.37)	25.2 (2.17)	27.7 (3.91)	25.7 (3.66)
Duration of HIV, y, median (range)	12 (1-39)	23 (6-34)	15 (6-44)	18 (9-28)
Duration of ART, y, median (range)	11 (1-28)	15 (5-28)	15 (3-35)	14 (8-25)
$CD4^+$ T cells, /μL, median (range)	801 (410-2166)	662 (370-1302)	880 (334-1787)	491 (380-781)

The Safety Analysis Set included all randomized participants who received ≥1 dose of study drug.
ABF, amtabafusp alfa; ART, antiretroviral therapy; MAD, multiple ascending dose; SAD, single ascending dose.

Safety

- TEAEs occurred in 46/54 (85%) PWH (**Table 2**)
  - Most TEAEs were Grade 1 or 2
  - Grade ≥3 TEAEs considered related to study drug by the investigator were experienced by 6/39 (15%) PWH who received ABF, including the following: pyrexia (n = 4), nausea (n = 1), vomiting (n = 1), and a transient decrease in $CD4^+$ lymphocytes (n = 1), which is common with T-cell engagers and reflects the redistribution of T cells to tissues[6]

Table 2. Summary of TEAEs

	SAD Cohort								MAD Cohort		
	ABF 0.3 mg (n = 1)	ABF 1 mg (n = 1)	ABF 3 mg (n = 1)	ABF 10 mg (n = 6)	ABF 30 mg (n = 6)	ABF 75 mg (n = 6)	ABF 150 mg (n = 5)	Placebo (n = 11)	ABF 30 mg Q2W (n = 6)	ABF up to 75 mg Q2W (n = 7)	Placebo (n = 4)
Any TEAE	1 (100)	1 (100)	1 (100)	5 (83)	5 (83)	6 (100)	5 (100)	8 (73)	5 (83)	7 (100)	2 (50)
Grade ≥3	1 (100)	0	0	0	2 (33)	1 (17)	1 (20)	0	0	4 (57)	0
Any treatment-related TEAE	1 (100)	0	1 (100)	0	4 (67)	5 (83)	5 (100)	2 (18)	3 (50)	7 (100)	1 (25)
Grade ≥3	0	0	0	0	2 (33)	0	1 (20)	0	0	3 (43)	0
CRS (all Grade 1)[a]	0	0	0	0	2 (33)	4 (67)	3 (60)	0	2 (33)	2 (29)	0
Dermatologic TEAE (all Grade 1 or 2)[b]	1 (100)	1 (100)	0	0	2 (33)	5 (83)	4 (80)	3 (27)	3 (50)	4 (57)	1 (25)
TEAE leading to premature discontinuation of study drug[c]	0	0	0	0	0	0	0	0	0	2 (29)	0
Any serious TEAE[d]	1 (100)	0	0	0	0	1 (17)	0	0	0	1 (14)	0
Death	0	0	0	0	0	0	0	0	0	0	0
Treatment-related serious TEAE[d]	0	0	0	0	0	0	0	0	0	0	0

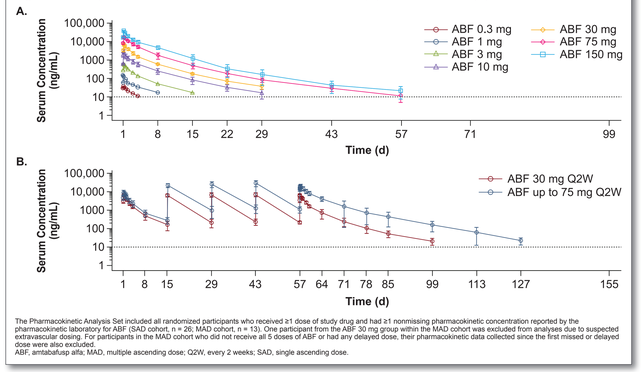
The Safety Analysis Set included all randomized participants who received ≥1 dose of study drug.
[a]Among PWH receiving ABF in the SAD cohort, pyrexia was observed in 9 (35%) PWH, headache was observed in 6 (23%) PWH, chills were observed in 5 (19%) PWH, and nausea was observed in 4 (15%) PWH. Among PWH receiving ABF in the MAD cohort, pyrexia was observed in 3 (23%) PWH, headache was observed in 3 (23%) PWH, chills were observed in 2 (15%) PWH, and nausea was observed in 3 (23%) PWH. [b]Among PWH receiving ABF in the SAD cohort, pruritus was observed in 5 (19%) PWH, skin exfoliation was observed in 5 (19%) PWH, and rash was observed in 4 (15%) PWH. Among PWH receiving placebo in the SAD cohort, pruritus was observed in 1 (9%) PWH and skin exfoliation was observed in 1 (9%) PWH. Among PWH receiving ABF in the MAD cohort, pruritus was observed in 2 (15%) PWH, skin exfoliation was observed in 3 (23%) PWH, and rash was observed in 1 (8%) PWH.
[c]Two PWH in the MAD cohort had TEAEs leading to premature discontinuation of study drug. One PWH had Grade 3 nausea and Grade 3 vomiting in the setting of CRS with Grade 2 elevated AST and ALT after one 30 mg dose of ABF. Another PWH had Grade 2 swelling face and Grade 2 urticaria with underlying medical history of chronic intermittent urticaria and rash after one 30 mg dose of ABF.
[d]A serious TEAE was defined as any event that resulted in death, a life-threatening situation, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or a medically important event or reaction.
ABF, amtabafusp alfa; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; MAD, multiple ascending dose; PWH, people with HIV; Q2W, every 2 weeks; SAD, single ascending dose; TEAE, treatment-emergent adverse event.

- Among those who received ABF, cytokine release syndrome (CRS) occurred in 13/39 (33%) PWH (all Grade 1) and reversible dermatologic TEAEs occurred in 20/39 (51%) PWH (all Grade 1 or 2; **Table 2**)
  - The frequencies of CRS and dermatologic TEAEs were generally dose dependent up to 150 mg, and their severity did not worsen with multiple doses
- There were no serious TEAEs considered related to study drug

Pharmacokinetics

- ABF showed linear pharmacokinetics at doses between 10 and 150 mg (**Figure 3**; **Table 3**)

Figure 3. Mean (SD) Serum ABF Concentration Over Time for the (A) SAD Cohort and (B) MAD Cohort



The Pharmacokinetic Analysis Set included all randomized participants who received ≥1 dose of study drug and had ≥1 nonmissing pharmacokinetic concentration reported by the pharmacokinetic laboratory for ABF (SAD cohort, n = 26; MAD cohort, n = 13). One participant from the ABF 30 mg group within the MAD cohort was excluded from analyses due to suspected extravascular dosing. For participants in the MAD cohort who did not receive all 5 doses of ABF or had any delayed dose, their pharmacokinetic data collected since the first missed or delayed dose were also excluded.
ABF, amtabafusp alfa; MAD, multiple ascending dose; Q2W, every 2 weeks; SAD, single ascending dose.

- Serum ABF pharmacokinetic parameters for the SAD and MAD cohorts are summarized in **Tables 3** and **4**, respectively
  - In the SAD cohort, elimination half-life ($t_{1/2}$) was 6.04 to 10.1 days following single doses of ABF 10 to 150 mg (**Table 3**)
  - In the MAD cohort, $t_{1/2}$ was 9.85 days for the ABF 30 mg group and 11.1 days for the ABF up to 75 mg group after the fifth dose (**Table 4**)

Table 3. Serum ABF Pharmacokinetic Parameters for the SAD Cohort

	0.3 mg (n = 1)	1 mg (n = 1)	3 mg (n = 1)	10 mg (n = 6)	30 mg (n = 6)	75 mg (n = 6)	150 mg (n = 5)
AUC_{last}, d*μg/mL	0.0584	0.257	1.39	6.50 (2.10)	17.1 (1.93)	53.3 (10.7)	106 (15.0)
AUC_{inf}, d*μg/mL	0.0934	0.331	1.48	6.65 (2.13)	17.3 (1.97)	53.6 (10.7)	107 (14.9)
C_{max}, μg/mL	0.0377	0.150	0.667	2.59 (1.12)	6.51 (1.76)	18.0 (3.01)	37.1 (4.04)
$t_{1/2}$, d	2.15	3.03	3.77	6.61 (2.01)	6.04 (1.81)	9.42 (1.53)	10.1 (4.71)
CL, L/d	3.21	3.02	2.02	1.73 (0.884)	1.75 (0.199)	1.45 (0.301)	1.42 (0.179)
V_{ss}, L	9.79	12.1	8.75	9.16 (2.91)	8.92 (2.52)	7.31 (0.928)	7.75 (1.74)

The Pharmacokinetic Analysis Set included all randomized participants who received ≥1 dose of study drug and had ≥1 nonmissing pharmacokinetic concentration reported by the pharmacokinetic laboratory for ABF (SAD cohort, n = 26). Data are reported as mean (SD).
ABF, amtabafusp alfa; AUC_{inf}, area under the concentration versus time curve extrapolated to infinite time; AUC_{last}, area under the concentration versus time curve from time zero to the last quantifiable concentration; CL, clearance; C_{max}, maximum observed concentration; SAD, single ascending dose; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state.

Table 4. Serum ABF Pharmacokinetic Parameters for the MAD Cohort

	30 mg		Up to 75 mg	
	Dose 1: 30 mg (n = 5)	Dose 5: 30 mg (n = 4)	Dose 1: 30 mg (n = 7)	Dose 5: 75 mg (n = 3)
AUC_{last}, d*μg/mL	15.7 (3.61)	20.3 (4.99)	22.4 (7.37)	98.7 (31.2)
AUC_{tau}, d*μg/mL	15.7 (3.61)	18.1 (4.16)	22.4 (7.37)	80.1 (22.5)
C_{max}, μg/mL	6.65 (0.974)	6.48 (1.37)	9.26 (2.64)	21.5 (4.16)
$t_{1/2}$, d	–	9.85 (1.72)	–	11.1 (3.28)
CL_{ss}, L/d	–	1.74 (0.457)	–	0.996 (0.317)
V_{ss}, L	–	9.23 (2.13)	–	7.18 (0.947)

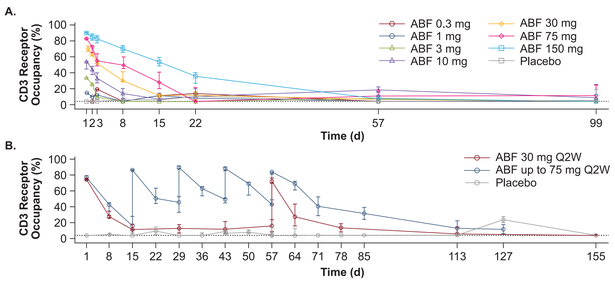
The Pharmacokinetic Analysis Set included all randomized participants who received ≥1 dose of study drug and had ≥1 nonmissing pharmacokinetic concentration reported by the pharmacokinetic laboratory for ABF (MAD cohort, n = 13). One participant from the ABF 30 mg group within the MAD cohort was excluded from analyses due to suspected extravascular dosing. For participants in the MAD cohort who did not receive all 5 doses of ABF or had any delayed dose, their pharmacokinetic data collected since the first missed or delayed dose were also excluded. Data are reported as mean (SD).
ABF, amtabafusp alfa; AUC_{last}, area under the concentration versus time curve from time zero to the last quantifiable concentration; AUC_{tau}, area under the concentration versus time curve over the dosing interval; CL_{ss}, clearance at steady state; C_{max}, maximum observed concentration; MAD, multiple ascending dose; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state.

- The median ABF accumulation ratio for area under the concentration versus time curve for PWH receiving ABF 30 mg Q2W was 1.10 (minimum, 1.07; maximum, 1.14; n = 4), indicating minimal accumulation with multiple Q2W dosing

Pharmacodynamics

- Among PWH who received ABF ≥10 mg in the SAD cohort, CD3 receptor occupancy in $CD2^+$ T cells peaked at 1 to 2 hours post infusion and returned to baseline between Days 15 and 57, depending on dose (**Figure 4A**)
  - At 2 hours post infusion, median CD3 receptor occupancy in $CD2^+$ T cells ranged from 54.6% for ABF 10 mg to 90.5% for ABF 150 mg, indicating T-cell engagement
  - No CD3 receptor occupancy accumulation was observed after multiple dosing (**Figure 4B**)

Figure 4. Median (Q1, Q3) CD3 Receptor Occupancy in $CD2^+$ T Cells Over Time in the (A) SAD Cohort and (B) MAD Cohort



The Pharmacodynamic Analysis Set included all randomized participants who received ≥1 dose of study drug and had ≥1 nonmissing value for CD3 receptor occupancy evaluation (N = 54). One participant from the ABF 30 mg group within the MAD cohort was excluded from analyses due to suspected extravascular dosing. For participants in the MAD cohort who did not receive all 5 doses of ABF or had any delayed dose, their pharmacodynamic data collected since the first missed or delayed dose were also excluded.
ABF, amtabafusp alfa; MAD, multiple ascending dose; Q1, first quartile; Q2W, every 2 weeks; Q3, third quartile; SAD, single ascending dose.

Limitations

- The current study had a relatively small sample size; larger studies are needed to confirm the safety results reported here
- Additional studies are needed to understand the efficacy of ABF treatment in PWH

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