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Pharmacokinetics, Pharmacodynamics, and Safety of Budigalimab, an Anti-PD-1 Monoclonal Antibody, in People Living with HIV-1

Tanaya R. Vaidya[1] | Preethi Krishnan[1] | Ana G Pires dos Santos[1] | Till Geib[1] | Fei Zhou[1]
Heide Betman[1] | Moti Ramgopal[2] | Jean-Pierre Routy[3] | Mohamad Shebley[1] | Nael M. Mostafa[1]

[1]AbbVie, Inc., North Chicago, IL, USA, [2]Midway Immunology & Research Center, Fort Pierce, FL, USA, [3]McGill University Health Centre, Montreal, QC, Canada

OBJECTIVES

- To evaluate low doses of budigalimab (25- to 250-fold) than those used for oncology indications to maximize safety and tolerability in a new target patient population i.e., people living with human immunodeficiency virus (HIV)-1 (PLWH) without malignancy
- To characterize pharmacokinetics (PK) and immunogenicity following single intravenous (IV) and subcutaneous (SC) and multiple IV doses of budigalimab in PLWH suppressed on antiretroviral therapy (ART) or undergoing analytical treatment interruption (ATI)
- To assess pharmacodynamics (PD) (i.e. programmed cell death [PD-1] receptor saturation [RS]) following budigalimab administration
- To evaluate safety, particularly immune related adverse events (irAEs), following budigalimab administration

CONCLUSIONS

Apparent half-life ($t_{1/2}$) following budigalimab admininistration 10 mg IV once every two weeks (Q2W) x 4 doses in PLWH was approximately 8 days

Almost complete PD-1 RS was observed for about 70 days with 10 mg IV Q2W x 4 doses, which was associated with efficacy signals (viral load control)

No serious adverse events (AEs) and no Grade 3 or higher AEs related to study drug were observed

PK/PD and safety data in the 10 mg IV Q2W and 20 mg SC treatment arms in Phase 1b demonstrate a favorable profile of budigalimab to continue development in Phase 2 in PLWH

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American College of Clinical Pharmacology Annual Meeting; 8 – 10 September 2024

AbbVie and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

AbbVie funded these studies and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. TRV, PK, AGPdS, TG, FZ, HB, MS and NMM are employees of AbbVie, Inc. and may own AbbVie, Inc. stock or stock options. MR is a speaker for AbbVie, Gilead Sciences, ViiV Healthcare, and Janssen and a consultant for Gilead Sciences, ViiV Healthcare, Merck, and Abbott. JPR is a speaker and consultant for AbbVie, Gilead Sciences, Merck & Co, Moderna, ViiV Healthcare. Copy editing was provided by Darby Dammeier of AbbVie.

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INTRODUCTION

- HIV-1 infection is a chronic condition that remains a major global health problem, with an estimated 39 million people world-wide living with the disease in 2022[1]
- There is a significant unmet need for treatment options that have a finite duration of therapy that could lead to sustained immune-mediated viral suppression and obviate the need for life-long daily use of ARTs in PLWH
- Budigalimab is a humanized, recombinant, Fc mutated immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeting the PD-1 receptor that was evaluated in Phase 1b trials in PLWH at doses 25- to 250-fold lower than those being evaluated for oncology indications
- Budigalimab is hypothesized to facilitate viral clearance and control chronic viral infection via reversal of T cell exhaustion and restoration of HIV-specific cellular immune responses through its mechanism of action[2]
- Known AEs of PD-1 inhibitors in oncology (regardless of HIV status) include irAEs[3,4]. However, occurrence of irAEs in the HIV indication with low doses of PD-1 inhibitors is not yet well understood.

METHODS

- PK, PD, and safety of budigalimab were evaluated in two randomized placebo-controlled Phase 1b studies in PLWH (NCT04799353 [Study 1] and NCT04223804 [Study 2])[5,6]
- Key eligibility criteria included
  - Positive test result for anti-HIV antibody (Ab) at screening
  - Cluster of differentiation (CD) 4 cell count ≥ 450 cells/µL (Study 1) or ≥ 500 cells/µL (Study 2) at screening and at least once during the 12 months prior to screening
  - Plasma HIV-1 RNA below lower limit of quantitation (LLOQ) at screening and for at least 6 months prior to screening
  - Negative HIV-2 Ab at screening
- PK data was evaluated using non-compartmental analyses
- Dose-proportionality was investigated using an analysis of covariance (ANCOVA) of the log-transformed dose-normalized exposure metrics for the 10 mg and 20 mg SC doses and the 2 mg and 10 mg IV doses
- Immunogenicity, safety, and the percentage and duration of PD-1 RS were evaluated for all treatment arms in Studies 1 and 2
- Exploratory efficacy (viral load kinetics) was evaluated in Study 2 during the ATI period

Figure 1. Study 1 Schematic: PK, PD, and Safety Following Single IV and SC Doses of Budigalimab in PLWH

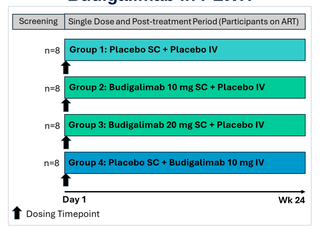
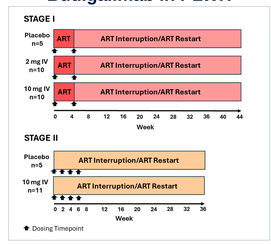


Figure 2. Study 2 Schematic: PK, PD, and Safety Following Multiple IV Doses of Budigalimab in PLWH



RESULTS

Pharmacokinetics and Pharmacodynamics

Study 1

- Following single dose administration of budigalimab, time to maximum observed concentration (T_{max}) occurred at a median of approximately 8 days, 6 days, and 0.25 h for the 10 mg SC, 20 mg SC, and 10 mg IV doses, respectively, while apparent terminal elimination half-life ($t_{1/2}$) was approximately 6.5, 9, and 8 days, respectively
- Dose-proportionality assessment (for maximum observed concentration [C_{max}] and area under the curve [AUC] from time 0 until the last observable concentration [AUC_t]) demonstrated that exposures following 20 mg SC dosing were more than dose-proportional relative to exposures following 10 mg SC dosing
- Bioavailability following SC administration (based on AUC from time 0 to infinity [AUC_{inf}]) was approximately 53% and 62% for the 10 mg and 20 mg SC doses
- Almost complete (> 95%) PD-1 RS on CD8+ T cells was observed for a median duration of 14, 42, and 35 days for the 10 mg SC, 20 mg SC, and 10 mg IV dose groups, respectively. Two participants (one each in the 10 mg SC and 20 mg SC groups) had all budigalimab concentrations below the LLOQ and therefore had incomplete PD-1 RS.

Safety

- There have been no serious adverse events, no Grade 3 or higher AEs related to the study drug, and no deaths reported in either of the HIV studies
- Budigalimab was generally well-tolerated. No infusion-related AEs have been reported in either study and no injection site reactions have been reported for SC arms in Study 1. Only three irAEs have been reported (described below), and no irAE reported was Grade 3 or higher:[5]
  - In Study 1, one participant in the 20 mg SC group experienced a non-serious, Grade 2, reversible irAE of lichenoid keratosis
  - In Study 2, one participant in the 10 mg IV Q4W group experienced a non-serious, Grade 1, reversible irAE of thyroiditis and one participant in the 10 mg IV Q2W group experienced a non-serious, Grade 1, reversible irAE of hyperthyroidism
- No apparent exposure-response relationships for irAEs were observed

Table 1. Study 1: Geomean Pharmacokinetic Parameters (Mean, CV%) of Budigalimab

PK Parameters (unit)	10 mg SC (N = 7)[c]	20 mg SC (N = 7)[c]	20 mg IV (N = 8)
C_{max} *(µg/mL)*	0.37 (0.49, 74)	1.57 (1.61, 20)	3.2 (3.3, 26)
T_{max}[a] *(h)*	195 (147 – 312)	147 (46.3 – 336)	0.25 (0.25 – 4.0)
$t_{1/2}$[b] *(day)*	6.47[d]	9.32 (4.03)[e]	8.02 (3.79)
AUC_t *(µg•day/mL)*	5.69 (8.95, 94)	34.0 (34.8, 23)	30.4 (34.2, 49)
AUC_{inf} *(µg•day/mL)*	23.9[d]	43.1 (43.3, 13)[f]	32.4 (36.3, 49)
C_{max}/Dose *(µg/mL/mg)*	0.04 (0.05, 74)	0.079 (0.08, 20)	0.32 (0.33, 26)
AUC_t/Dose *(µg•day/mL/mg)*	0.57 (0.9, 94)	1.70 (1.74, 23)	3.04 (3.42, 49)
AUC_{inf}/Dose *(µg•day/mL/mg)*	2.39[d]	2.15 (2.17, 13)[f]	3.24 (3.63, 49)

CV = coefficient of variation
a. T_{max} presented as median and range; b. $t_{1/2}$ presented as harmonic mean and pseudo standard deviation; c. One participant had all budigalimab concentrations below the LLOQ and was excluded from the analysis; d. N = 1; e. N = 4; f. N = 3.

Study 2

- Following multiple dose administration of budigalimab, $t_{1/2}$ was approximately 3 – 5 days and 6 days for the 2 mg and 10 mg IV once every four weeks (Q4W) regimens in Stage I. In Stage II, $t_{1/2}$ was approximately 8 days following 10 mg IV administered every two weeks (Q2W) for four doses
- Dose-proportionality assessment showed that exposures following 10 mg IV dosing were more than dose-proportional relative to 2 mg IV dosing, indicating non-linear PK characteristic of target mediated drug disposition
- Negligible accumulation was observed with a Q4W dosing interval, and approximately 2-fold accumulation was observed with a Q2W dosing interval
- Almost complete (> 95%) PD-1 RS on CD8+ T cells after each dose was observed for a median duration of 15 days, 29 days, and 29.5 days for the 2 mg IV Q4W, 10 mg IV Q4W and 10 mg IV Q2W regimens. This resulted in a total duration of > 95% PD-1 RS for about 70 days with the 10 mg IV Q2W x 4 doses regimen, which was associated with efficacy signals.
- In Stage II, 6 of 11 participants had delay in viral rebound and/or reached and sustained ART-free viral control (HIV-1 RNA < 200 copies/mL) for at least 6 weeks post ATI, with 2 of 11 participants continuing to sustain ART-free viral control until the end of the study. None of the participants that received placebo demonstrated HIV-1 RNA control < 200 copies/mL after rebound and during ATI[5,6]
- No apparent exposure-response relationships for viral load control were observed

Table 2A. Study 2 Stage I: Geomean Pharmacokinetic Parameters (Mean, CV%) of Budigalimab

PK Parameter (unit)	Following Dose 1 (Study Day 1) 2 mg IV (N = 10)[c]	Following Dose 1 (Study Day 1) 10 mg IV (N = 10)[f]	Following Dose 2 (Study Week 4) 2 mg IV (N = 9)[c]	Following Dose 2 (Study Week 4) 10 mg IV (N = 9)[f]
C_{max} *(µg/mL)*	0.602 (0.65, 31)	3.57 (3.69, 30)	0.684 (0.719, 30)[h]	3.2 (3.39, 31)[h]
T_{max}[a] *(h)*	3.4 (1.5 – 167)	2.6 (1.3 – 5.5)	1.6 (1.3 – 3.1)[h]	1.3 (1.1 – 191)[h]
AUC_{tau} *(µg•day/mL)*	3.48 (3.68, 43)[d]	32 (35, 49)	4.07 (4.37, 43)[i]	33.5 (35.7, 34)[h]
AUC_{inf} *(µg•day/mL)*	3.13 (3.13, 8)[e]	39.7 (48.1, 77)[g]	NR	NR
C_{max}/Dose *(µg/mL/mg)*	0.301 (0.325, 31)	0.357 (0.369, 30)	0.342 (0.359, 30)[h]	0.32 (0.339, 31)[h]
AUC_{tau}/Dose *(µg•day/mL/mg)*	1.74 (1.84, 43)[d]	3.2 (3.5, 49)	2.04 (2.18, 43)[i]	3.35 (3.57, 34)[h]
AUC_{inf}/Dose *(µg•day/mL/mg)*	1.56 (1.57, 8)[e]	3.97 (4.81, 77)[g]	NR	NR
$t_{1/2}$[b] *(day)*	NR	NR	3.24, 4.62[j]	5.57 (1.09)[k]

AUC_{tau} = AUC over the dosing interval; NR = not reported
a. T_{max} presented as median (minimum – maximum); b. $t_{1/2}$ presented as harmonic mean and pseudo standard deviation; c. One participant in the 2 mg group prematurely discontinued prior to the second dose and was not included in the Dose 2 summary; d. N = 6; e. N = 4; f. One participant in the 10 mg group was excluded from the Dose 2 summary as they had a dosing interval error (i.e., Dose 2 was delayed by 3 weeks); g. N = 5; h. N = 9; i. N = 8; j. N ≤ 2 are presented as individual values; k. N = 7.

Table 2B. Study 2 Stage II: Geomean Pharmacokinetic Parameters (Mean, CV%) of Budigalimab

PK Parameter (unit)	10 mg IV Q2W (N = 11) Dose 1 (Study Day 1)	10 mg IV Q2W (N = 11) Dose 4 (Study Week 6)[c]
C_{max} *(µg/mL)*	3.1 (3.35, 43)	4.35 (4.55, 33)[d]
T_{max}[a] *(h)*	2.4 (0.6 – 4.8)	1.5 (0.6 – 2.6)[d]
AUC_{tau} *(µg•day/mL)*	18 (19.9, 48)	36.7 (39.5, 44)[d]
C_{max}/Dose *(µg/mL/mg)*	0.31 (0.34, 43)	0.44 (0.46, 33)[d]
AUC_{tau}/Dose *(µg•day/mL/mg)*	1.8 (1.99, 48)	3.67 (3.95, 44)[d]
$t_{1/2}$[b] *(day)*	NR	7.99 (3.42)[e]

a. T_{max} presented as median (minimum – maximum); b. $t_{1/2}$ presented as harmonic mean and pseudo standard deviation; c. Two participants who only received the first two doses were excluded from the summary for Dose 4; d. N = 9; e. N = 6.

Figure 3. Study 1: Pharmacokinetics and Pharmacodynamics (% Free PD-1+/CD8+ T cells) of Budigalimab

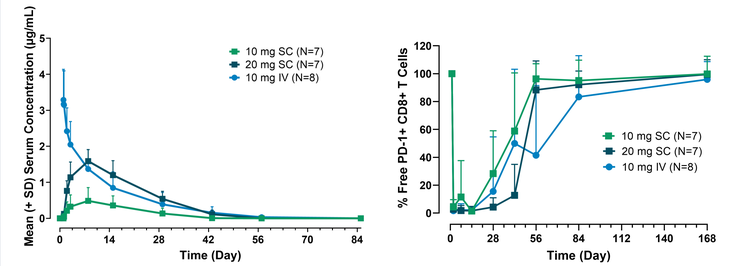


Figure 4. Study 2: Pharmacokinetics and Pharmacodynamics (% Free PD-1+/CD8+ T cells) of Budigalimab

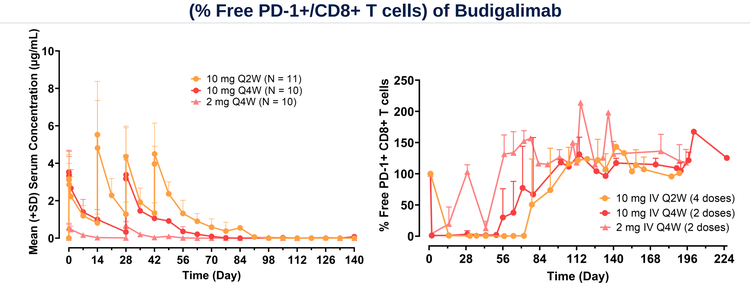


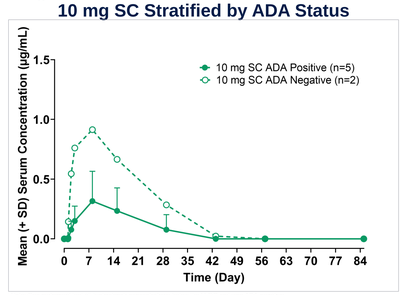
Table 3. Incidence of Treatment-Emergent ADA Across Studies 1 and 2

Study	Study 1			Study 2		
Treatment Arm	10 mg SC	20 mg SC	10 mg IV	2 mg IV Q4W	10 mg IV Q4W	10 mg IV Q2W
ADA Incidence % (n/N)	63% (5/8)	0% (0/8)	38% (3/8)	40% (4/10)	50% (5/10)	64% (7/11)

Immunogenicity

- The incidence of antidrug antibodies (ADA) across Studies 1 and 2 is presented in Table 3. Except for the 20 mg SC group in Study 1, all active treatment arms had some participants with incidence of ADA
- Overall, no apparent impact of ADA on budigalimab PK was observed across the IV groups (data not shown), whereas a trend towards lower exposures due to ADA was observed in the 10 mg SC group (Figure 5)

Figure 5. Pharmacokinetics of Budigalimab 10 mg SC Stratified by ADA Status



Note: One participant had all budigalimab concentrations below the LLOQ and was ADA-negative.