Evaluation of Therapeutic Concentrations of Anti-HIV Antibodies 3BNC117/Teropavimab and 10-1074/Zinlirvimab Through PK-PD Modeling and Prediction of the Washout Duration in HIV Cure Studies

Abstract TUPEB05

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Background

- 3BNC117 and 10-1074 are potent broadly neutralizing antibodies (bNAbs) isolated and cloned from people with HIV that bind to different epitopes on the HIV envelope glycoprotein
- Teropavimab (TAB; 3BNC117-LS) and zinlirvimab (ZAB; 10-1074-LS) are recombinant, fully human monoclonal antibodies derived from 3BNC117 and 10-1074, respectively, with 2 amino acid substitutions in the Fc domain to prolong their half-lives
- 3BNC117 and 10-1074 have been shown to induce rapid decline in viremia in people with HIV, as well as delay the time to viral rebound in suppressed people with HIV during analytical treatment interruption (ATI)[1-6]
- The combination of 3BNC117/TAB and 10-1074/ZAB, together with immune-modulating agents, is being investigated for its potential to eliminate the HIV reservoir and induce long-term remission in people with HIV. However, due to their potent viral neutralization effects, insufficient washout duration before ATI can confound the efficacy assessment of time to virologic rebound in HIV cure studies
- The purpose of this study was to characterize the pharmacokinetics (PK) and pharmacokinetic-pharmacodynamic (PK-PD) relationships of these bNAbs through PK-PD viral dynamic modeling, and to predict the required length of washout for TAB/ZAB in HIV cure studies in order to assess post-treatment viral control during ATI

Methods

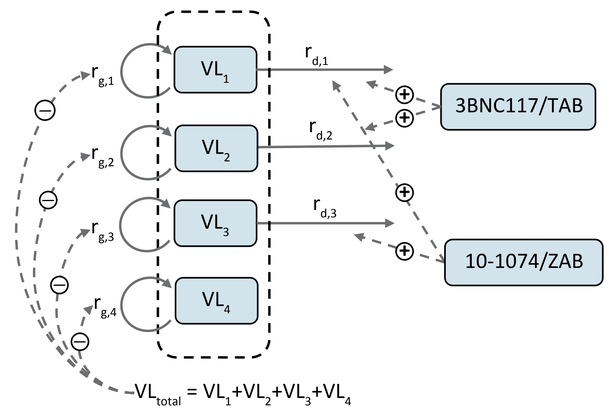
- Population PK and PK-PD models were developed using a nonlinear mixed-effect modeling approach based on serum bNAb concentration and/or viral dynamic data from 6 efficacy studies in people with HIV, and 3 PK studies of 3BNC117/TAB and/or 10-1074/ZAB (Table 1)
- bNAb concentrations were measured by ELISA assays, except for study NCT03526848.[6] For this study, concentrations measured by TZM-bl assay[11] were transformed to ELISA data using a log-linear correlation model calibrated based on data from study NCT02825797,[4,5] where PK were measured using both methods
- The PK data of the bNAbs were modeled by 2-compartment linear PK models. Covariates (demographics, disease status, combination treatment) were tested using stepwise forward addition (α = 0.01) and backward elimination (α = 0.001) methods
- The PK-PD model describes viral replication using a logistic growth function and viral elimination using first-order kinetics, with a nonlinear saturable (E_{max}) model to describe the relationship between bNAb concentrations and viral elimination rates. Distinct viral populations sensitive or resistant to each bNAb were modeled to capture the mechanism of resistance selection in treated participants (Figure 1)
- PK and PK-PD models were fitted sequentially. Model evaluations were performed using standard diagnostic plots and visual predictive checks
- Simulations were performed to predict PK and dynamics of viral rebound during ATI after different lengths of washout periods after TAB/ZAB dosing
- Modeling was conducted using Phoenix® NLME. Simulations and plotting were performed using R software

Table 1. Studies included in the PK-PD modeling

Study	Compound (dose)	Participants	Efficacy evaluation	N for PK	N for PD
NCT02018510[1]	3BNC117 (1, 3, 10, 30 mg/kg IV)	HIV negative	–	22	–
		Suppressed PWH	–	16	–
		Viremic PWH	Viral suppression	17	17
NCT02511990[2]	10-1074 (3, 10, 30 mg/kg IV)	HIV negative	–	14	–
		Suppressed PWH	–	3	–
		Viremic PWH	Viral suppression	15	15
NCT02446847[3]	3BNC117 (30 mg/kg IV)	Suppressed PWH	Viral rebound during ATI	15	14
NCT02824536[7]	3BNC117 + 10-1074 (3+3, 10+10 mg/kg IV)	HIV negative	–	18	–
NCT02825797[4,5]	3BNC117 + 10-1074 (30+30 mg/kg IV)	Viremic PWH	Viral suppression	7	–
		Suppressed PWH	Viral rebound during ATI	21	13
NCT03526848[6,a]	3BNC117 + 10-1074 (30+30 mg/kg IV)	Suppressed PWH	Viral rebound during ATI	26	22
NCT03254277 (part B)[8,b]	TAB (30 mg/kg IV, 150 or 300 mg SC)	HIV negative	–	15	–
		Suppressed PWH	–	3	–
NCT03554408[9]	ZAB alone (3, 10, 30 mg/kg IV, 140 or 280 SC) TAB + ZAB (30+30 mg/kg IV, 150-300 + 60-280 mg SC)	HIV negative	–	57	–
		Suppressed PWH	–	10	–
NCT04250636[10]	TAB + ZAB (30+30 mg/kg IV)	Viremic PWH	Viral suppression	6	6

ATI, analytical treatment interruption; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; PWH, people with HIV; SC, subcutaneous; TAB, teropavimab; ZAB, zinlirvimab.
[a]PK measured using TZM-bl assay was transformed to ELISA data and used for external model validation. [b]Only data from part B of this study were included due to the incomplete glycosylation of drug product used in part A of the study.

Figure 1. Schema of the PK-PD viral dynamic model



$$\frac{dVL_i}{dt} = r_{g,i} - r_{d,i}$$

$$r_{g,i} = k_g \times \left(1 - \frac{VL_{total}}{VL_{ss}}\right) \times VL_i$$

$$VL_i(0) = VL_{total}(0) \times f_i$$

$$(i = 1 \ldots 4)$$

$$r_{d,1} = \frac{k_{del,\,drug1} \times C_1/EC_{50,\,drug1} + k_{del,\,drug2} \times C_2/EC_{50,\,drug2}}{C_1/EC_{50,\,drug1} + C_2/EC_{50,\,drug2} + 1} \times VL_1$$

$$r_{d,2} = \frac{k_{del,\,drug1} \times C_1}{EC_{50,\,drug1} + C_1} \times VL_2$$

$$r_{d,3} = \frac{k_{del,\,drug2} \times C_2}{EC_{50,\,drug2} + C_2} \times VL_3$$

C_1 and C_2, serum concentration of 3BNC117/TAB and 10-1074/ZAB, respectively; $EC_{50,drug1}$ and $EC_{50,drug2}$, concentration that leads to 50% maximum effect of 3BNC117/TAB and 10-1074/ZAB, respectively; f_i, initial fraction of i^{th} viral compartment; k_g, maximal viral replication rate constant; $k_{del,drug1}$ and $k_{del,drug2}$, viral elimination rate constant for 3BNC117/TAB and 10-1074/ZAB, respectively; $r_{d,i}$, viral elimination rate for i^{th} viral compartment; $r_{g,i}$, viral replication rate for i^{th} viral compartment; TAB, teropavimab; VL_1, copies of viruses sensitive to both 3BNC117/TAB and 10-1074/ZAB; VL_2, copies of viruses sensitive to 3BNC117/TAB and resistant to 10-1074/ZAB; VL_3, copies of viruses sensitive to 10-1074/ZAB and resistant to 3BNC117/TAB; VL_4, copies of viruses resistant to both 3BNC117/TAB and 10-1074/ZAB (assumed to be 0); VL_{ss}, steady state viral load; VL_{total}, total viral load; ZAB, zinlirvimab.

Results

PK modeling

- The PK data of 3BNC117, 10-1074, TAB, and ZAB were well described by linear 2-compartment PK models (Figure 2)
- For 3BNC117 and 10-1074, the estimated half-lives were the longest in people without HIV, followed by suppressed people with HIV, and shortest in viremic people with HIV (Figure 3)
- For TAB and ZAB, the estimated half-lives were longer than those of 3BNC117 and 10-1074, similar between people without HIV and suppressed people with HIV (62 and 79 days for TAB and ZAB, respectively), and shorter in viremic people with HIV (46 and 55 days for TAB and ZAB, respectively) (Figure 3)

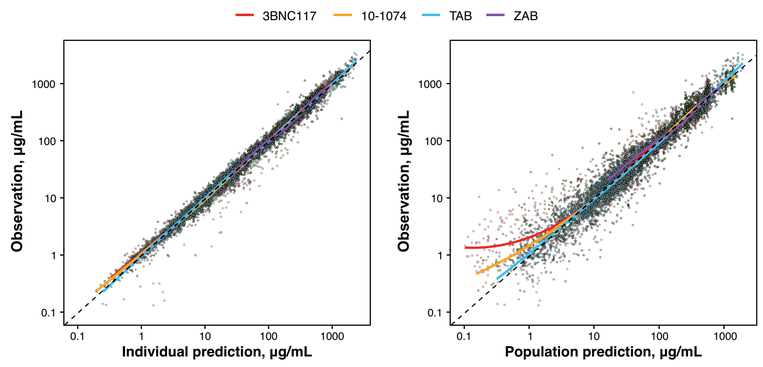
PK-PD modeling

- The PK-PD model adequately described the dynamics of viral suppression in viremic people with HIV after bNAb treatment with 3BNC117, 10-1074 alone at different doses and in combination, as well as combination treatment with TAB and ZAB (Figure 4)
- The model described the time to viral rebound during ATI after bNAb treatment with 3BNC117 alone or in combination with 10-1074 (Figure 5)
- The estimated mean serum concentrations corresponding to 50% maximum drug effect (EC_{50}) of 3BNC117/TAB and 10-1074/ZAB were 25.4 and 32.2 µg/mL, which correspond to EC_{20} of 6.35 and 8.06 µg/mL, respectively (Table 2)

PK-PD simulations

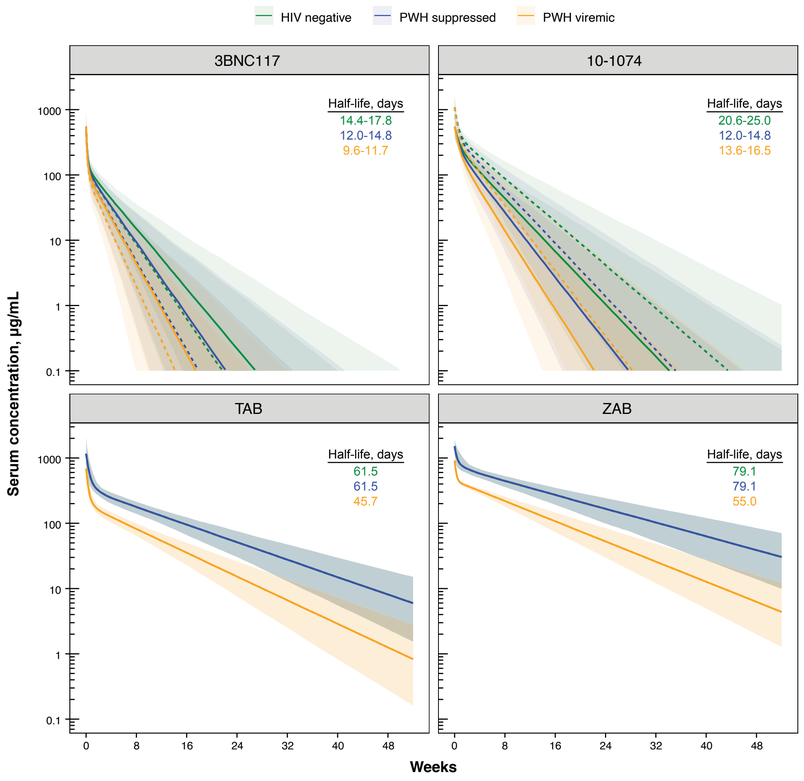
- PK-PD simulations predicted that after a washout period of ≥ 48 weeks after single-dose TAB and ZAB intravenous administration, the viral neutralization effects of these bNAbs would have minimal impact on the time to viral rebound during ATI (Figure 6)
- After single-dose 30 mg/kg TAB and 10 mg/kg ZAB intravenous administration, both bNAb concentrations were predicted to drop below their in vivo EC_{50} around similar times and maintain similar levels relative to the EC_{50} afterward, thus minimizing the risk of resistance development from functional monotherapy of either bNAb. At week 48, both bNAb concentrations were predicted to be lower than EC_{50} in over 90% of participants (Figure 7)

Figure 2. Observed vs predicted bNAb serum concentrations from the PK models



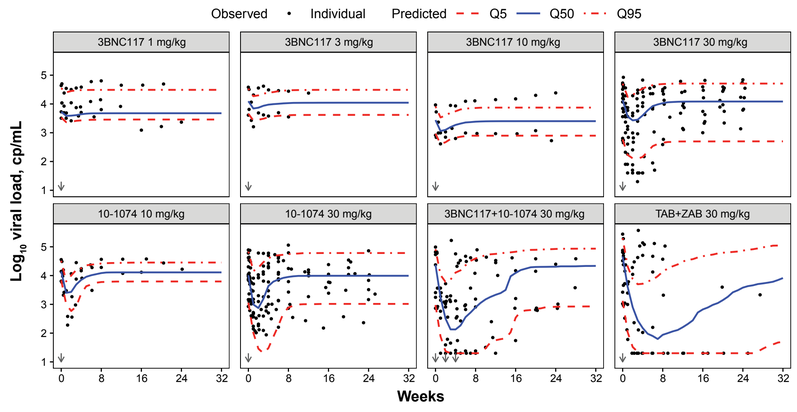
bNAb, broadly neutralizing antibody; PK, pharmacokinetic; TAB, teropavimab; ZAB, zinlirvimab.
Circles represent individual data. Solid lines represent LOESS (locally estimated scatterplot smoothing) fit. Dashed lines represent the line of identity.

Figure 3. Model-predicted PK profiles after single-dose 30 mg/kg IV infusion



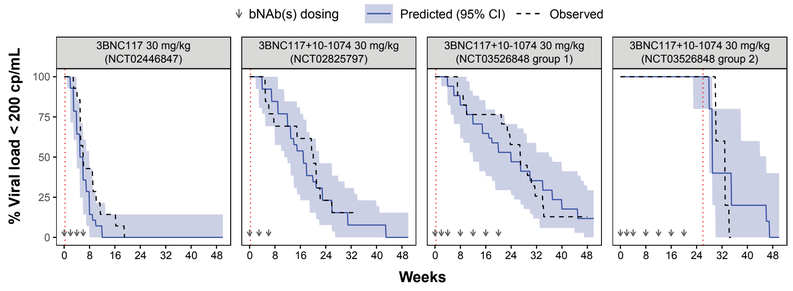
IV, intravenous; PK, pharmacokinetic; PWH, people with HIV; TAB, teropavimab; ZAB, zinlirvimab.
1000 virtual subjects were simulated using the population PK models of 3BNC117, 10-1074, TAB, and ZAB. Solid and dashed lines represent model-predicted medians for mono and combination therapy, respectively, and shaded areas represent the 90% prediction intervals of the population.

Figure 4. Model-predicted vs observed viral dynamics after bNAb treatment in viremic people with HIV



bNAb, broadly neutralizing antibody; Q5, 5th percentile; Q50, 50th percentile; Q95, 95th percentile; TAB, teropavimab; ZAB, zinlirvimab.
100 trial simulations were performed with the same number of subjects as the original dataset used for modeling fitting. The predicted quantiles were calculated from the median of the quantiles across all trial replicates. Arrows represent bNAb(s) dosing.

Figure 5. Model-predicted vs observed time to viral rebound during ATI after bNAb treatment



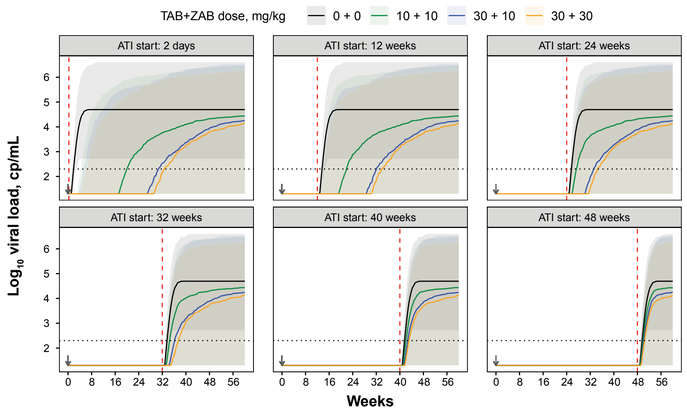
ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody; CI, confidence interval.
Doses in the ATI studies: NCT02446847, 2 doses of 30 mg/kg 3BNC117 every 3 weeks or up to 4 doses of 30 mg/kg 3BNC117 every 2 weeks; NCT02825797, up to 3 doses of 30 mg/kg 3BNC117 and 30 mg/kg 10-1074 every 3 weeks; NCT03526848, 30 mg/kg 3BNC117 and 30 mg/kg 10-1074 every 2 weeks for 3 doses followed by every 4 weeks for up to 4 doses (group 1, ATI started on day 2; group 2, ATI started at week 26 [1 participant started at week 21]). 100 trial simulations were performed with the same number of subjects as the original dataset used for model fitting. Solid blue lines (shaded region) represent the medians (2.5th to 97.5th percentiles) across all trial replicates. Arrows represent bNAb(s) dosing. Red dotted lines indicate start of ATI.

Table 2. Key PK-PD model parameter estimates

Parameter	Mean	95% CI	%CV
$EC_{50,\,3BNC117\ or\ TAB}$, µg/mL[a]	25.4	19.6-32.9	162
$EC_{50,\,10\text{-}1074\ or\ ZAB}$, µg/mL[b]	32.2	10.1-102.8	79.5
Viral replication rate constant, kg, day^{-1}	0.441	0.414-0.468	24.5
Viral elimination rate constant, $k_{del,\,3BNC117\ or\ TAB}$, day^{-1}	0.507	0.476-0.538	–
Viral elimination rate constant, $k_{del,\,10\text{-}1074\ or\ ZAB}$, day^{-1}	0.799	0.609-0.990	–

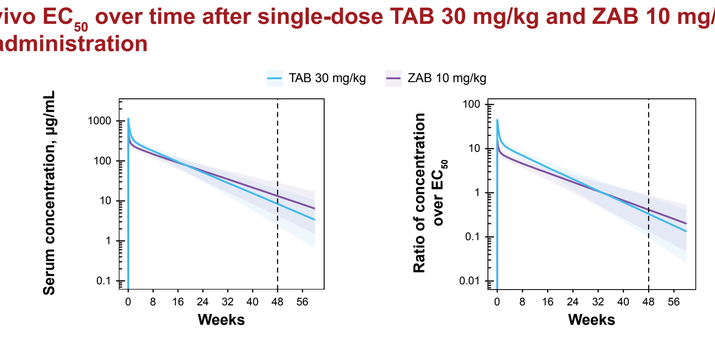
CI, confidence interval; CV, coefficient of variation; EC_{20}, concentration that leads to 20% maximum drug effect; EC_{50}, concentration that leads to 50% maximum drug effect; PD, pharmacodynamic; PK, pharmacokinetic; TAB, teropavimab; ZAB, zinlirvimab.
[a]Corresponds to mean (95% CI) EC_{20} value of 6.35 (4.90-8.22) µg/mL. [b]Corresponds to mean (95% CI) EC_{20} value of 8.06 (2.53-25.7) µg/mL.

Figure 6. Model-predicted viral rebound dynamics after single-dose TAB/ZAB combination treatment with different ATI start times



ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody; PD, pharmacodynamic; PK, pharmacokinetic; TAB, teropavimab; ZAB, zinlirvimab.
Dotted horizontal lines indicate the threshold for viral rebound (200 cp/mL). 1000 virtual subjects were simulated using the population PK-PD model. Solid lines represent model-predicted median, and shaded areas represent the 90% prediction intervals of the population. Arrows represent bNAb(s) dosing. Red dashed lines indicate start of ATI.

Figure 7. Simulated bNAb serum concentrations and their ratios over in vivo EC_{50} over time after single-dose TAB 30 mg/kg and ZAB 10 mg/kg IV administration



bNAb, broadly neutralizing antibody; EC_{50}, concentration that leads to 50% maximum drug effect; PD, pharmacodynamic; PK, pharmacokinetic; TAB, teropavimab; ZAB, zinlirvimab.
1000 virtual subjects were simulated using the population PK models. Solid lines represent model-predicted medians, and shaded areas represent the 90% prediction intervals of the population. Ratios were calculated based on the estimated EC_{50} values from the PK-PD model (25.4 µg/mL for TAB, 32.2 µg/mL for ZAB). Black dashed lines indicate the proposed earliest start time of ATI.

Conclusions

The population PK and PK-PD models were able to describe the PK and viral dynamic data from previous clinical studies of 3BNC117, 10-1074, TAB and ZAB

Based on the PK-PD model, a washout duration of 48 weeks after a single-dose administration of TAB 30 mg/kg and ZAB 10 mg/kg is recommended in order to minimize the direct antiviral effects of the bNAbs during ATI, thereby allowing a better assessment of efficacy of combination regimens in mediating treatment-free virologic control in HIV cure studies

References: **1.** Caskey M, et al. *Nature*. 2015;522:487-491. **2.** Caskey M, et al. *Nat Med*. 2017;23:185-191. **3.** Scheid JF, et al. *Nature*. 2016;535:556-560. **4.** Mendoza P, et al. *Nature*. 2018;561:479-484. **5.** Bar-On Y, et al. *Nat Med*. 2018;24:1701-1707. **6.** Gaebler C, et al. *Nature*. 2022;606:368-374. **7.** Cohen YZ, et al. *PLoS One*. 2019;14:e0219142. **8.** ClinicalTrials.gov. NCT03254277. https://clinicaltrials.gov/ct2/show/NCT03254277. Accessed May 2023. **9.** ClinicalTrials.gov. NCT03554408. https://clinicaltrials.gov/ct2/show/NCT03554408. Accessed May 2023. **10.** ClinicalTrials.gov. NCT04250636. https://clinicaltrials.gov/ct2/show/NCT04250636. Accessed May 2023. **11.** Sarzotti-Kelsoe M, et al. *J Immunol Methods*. 2014;409:131-146.

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Disclosures: **YZ**, **SEC**, **DSG**, and **RP** are employees of and may own stock in Gilead Sciences, Inc. **SG** is an employee and owner of POPPHARM. **MC** serves on an ad hoc advisory board to Gilead Sciences. **QM** reports no conflicts to disclose

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