# Pharmacokinetic interaction assessment of the HIV broadly neutralizing monoclonal antibody VRC07-523LS: a cross-protocol analysis of three phase 1 HIV prevention trials HVTN127/HPTN087, HVTN130/HPTN089 and HVTN136/HPTN092.

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# Conflict of Interest

- None

# Summary

**What is the main issue or key question(s) your work addresses?**

- The monoclonal antibody (mAb) VRC07-523LS is safe and has potent neutralization activity against HIV. We assessed whether there are differences in pharmacokinetics (blood levels over time and distribution in the body) when given in combination with other mAbs.

**What was the key finding or “take home message”?**

- The pharmacokinetics of VRC07-523LS are largely unaltered in combination administration compared to alone.

**How is this important for HIV vaccine research?**

- VRC07-523LS has favorable PK and is a good candidate for combination bnAb regimens.

# Background

Prior trials showed that VRC07-523LS alone or in combination with other bnAbs was:

- safe
- well-tolerated and
- has better PK and neutralization profile than VRCO1

Potential differences in PK of VRC07-523LS when given in combination vs. alone have not been formally assessed

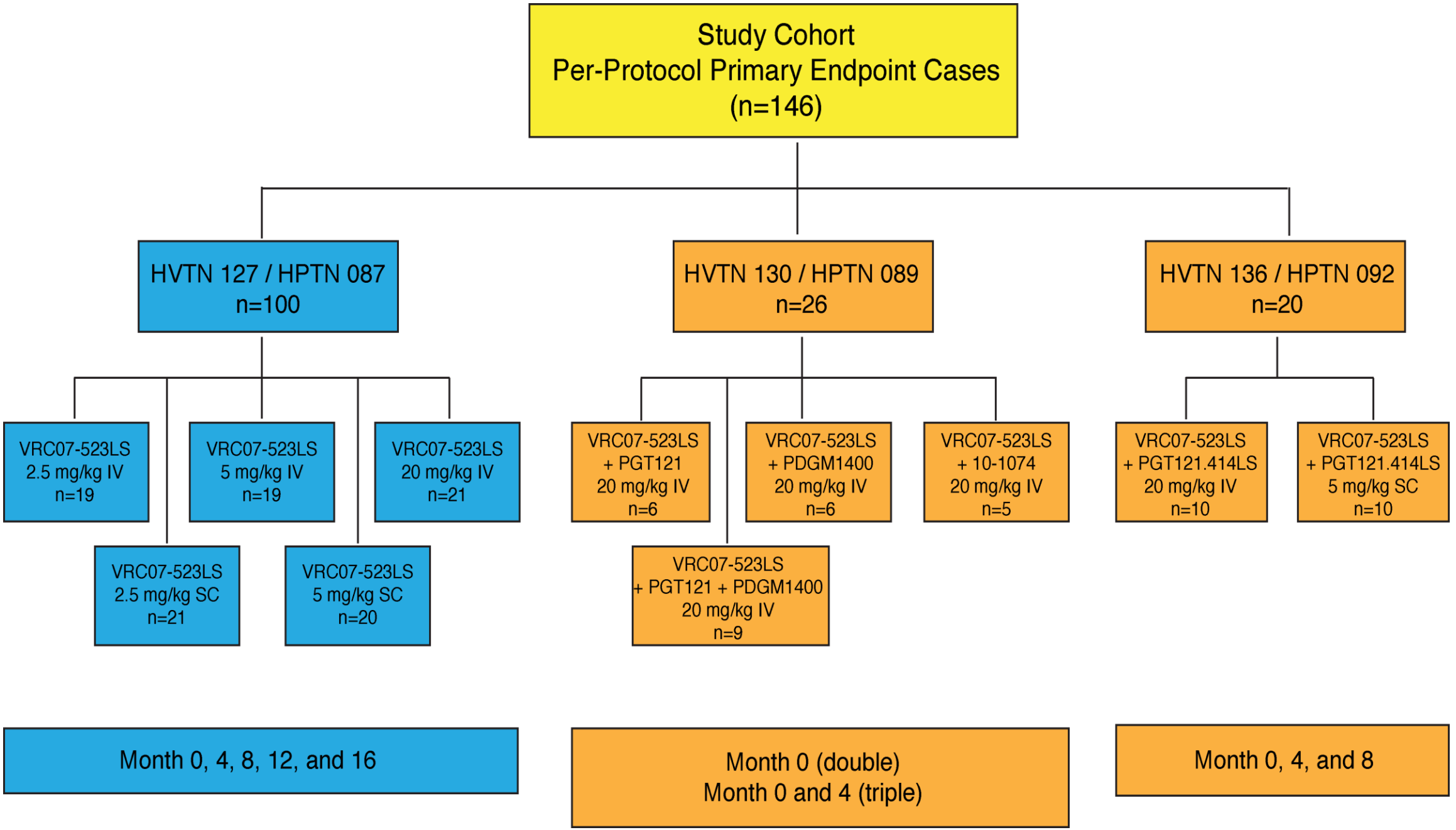
# Aim

- We performed a **cross-protocol analysis** integrating serum concentration data from 3 trials to compare the PK of VRC07-523LS when administered in combination with other mAbs vs. alone.

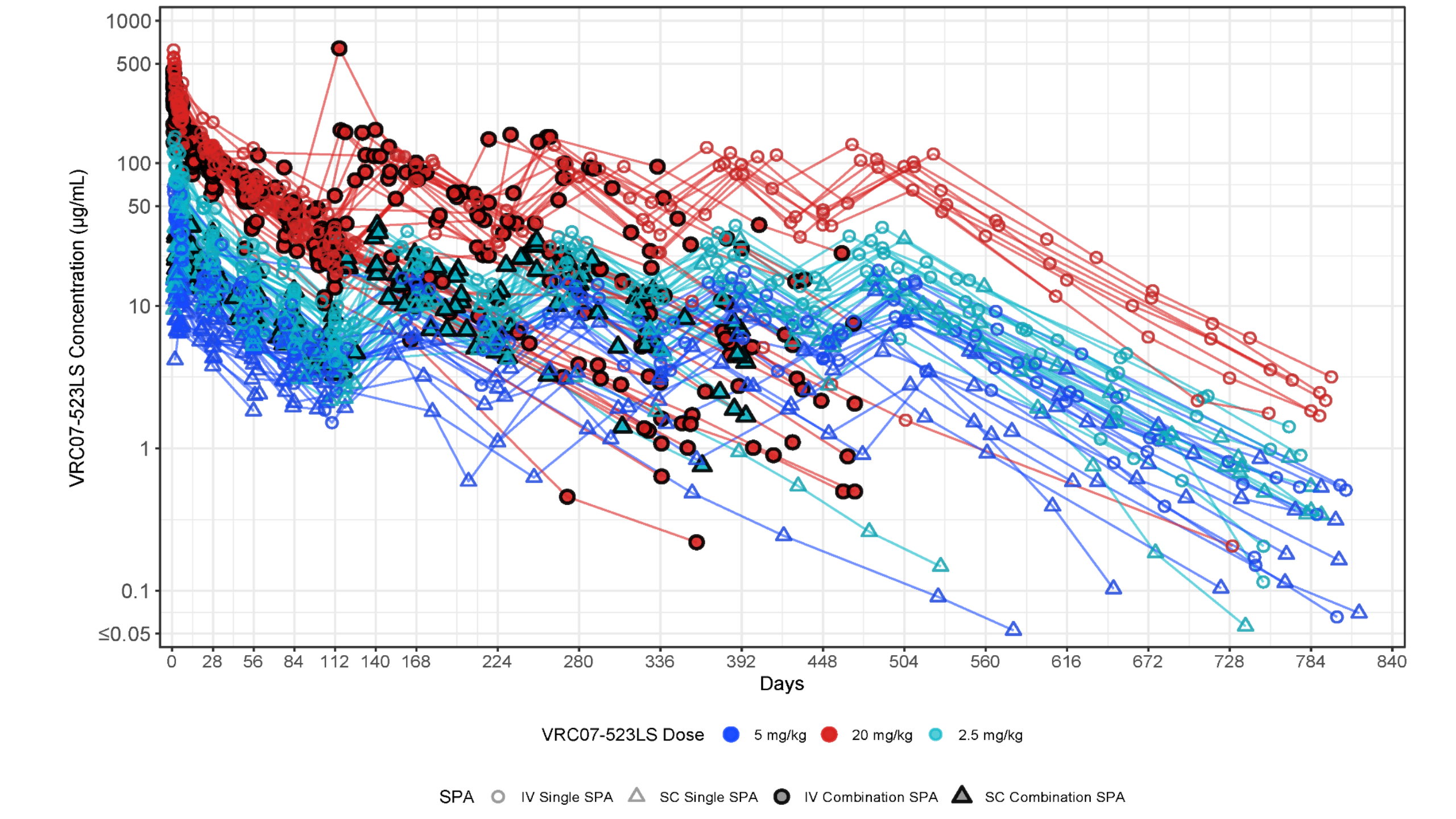
- We hypothesized that the overall PK profile of VRC07-523LS would be similar when administered in combination or alone.

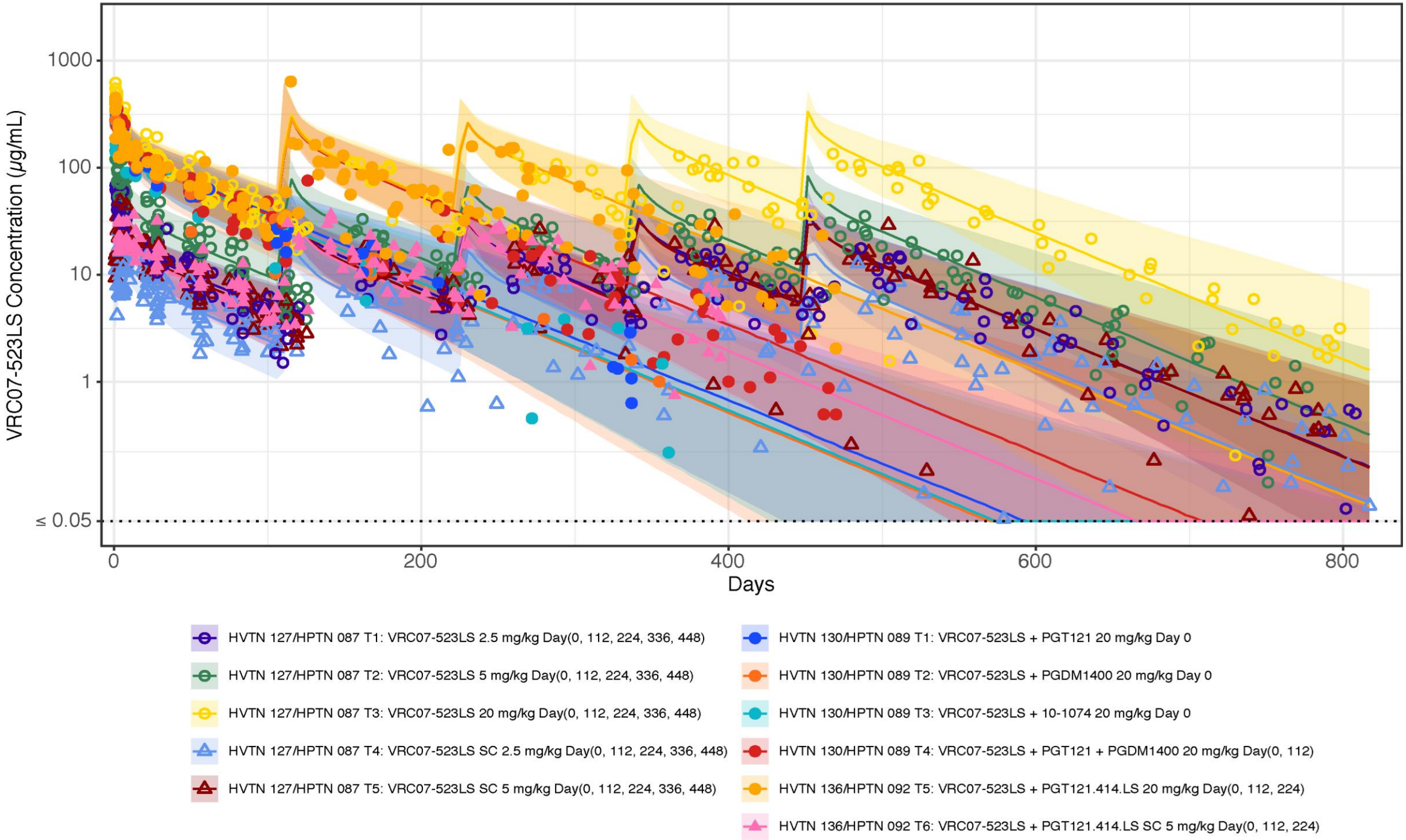
# Methods

- Retrospective cross-protocol analysis of the HVTN 127/HPTN 087, HVTN 130/HPTN 089 and HVTN 136/HPTN 092 studies
- Intravenous and subcutaneous administration included
- Serum concentrations of VRC07-523LS were described by an open two-compartment population PK model
- Participants divided into 2 groups based on combination or single VRC07-523LS administration
- Antibodies were administered sequentially
- PK parameters were compared using the targeted maximum likelihood estimation (TMLE) method to adjust for potential differences in baseline covariates between groups

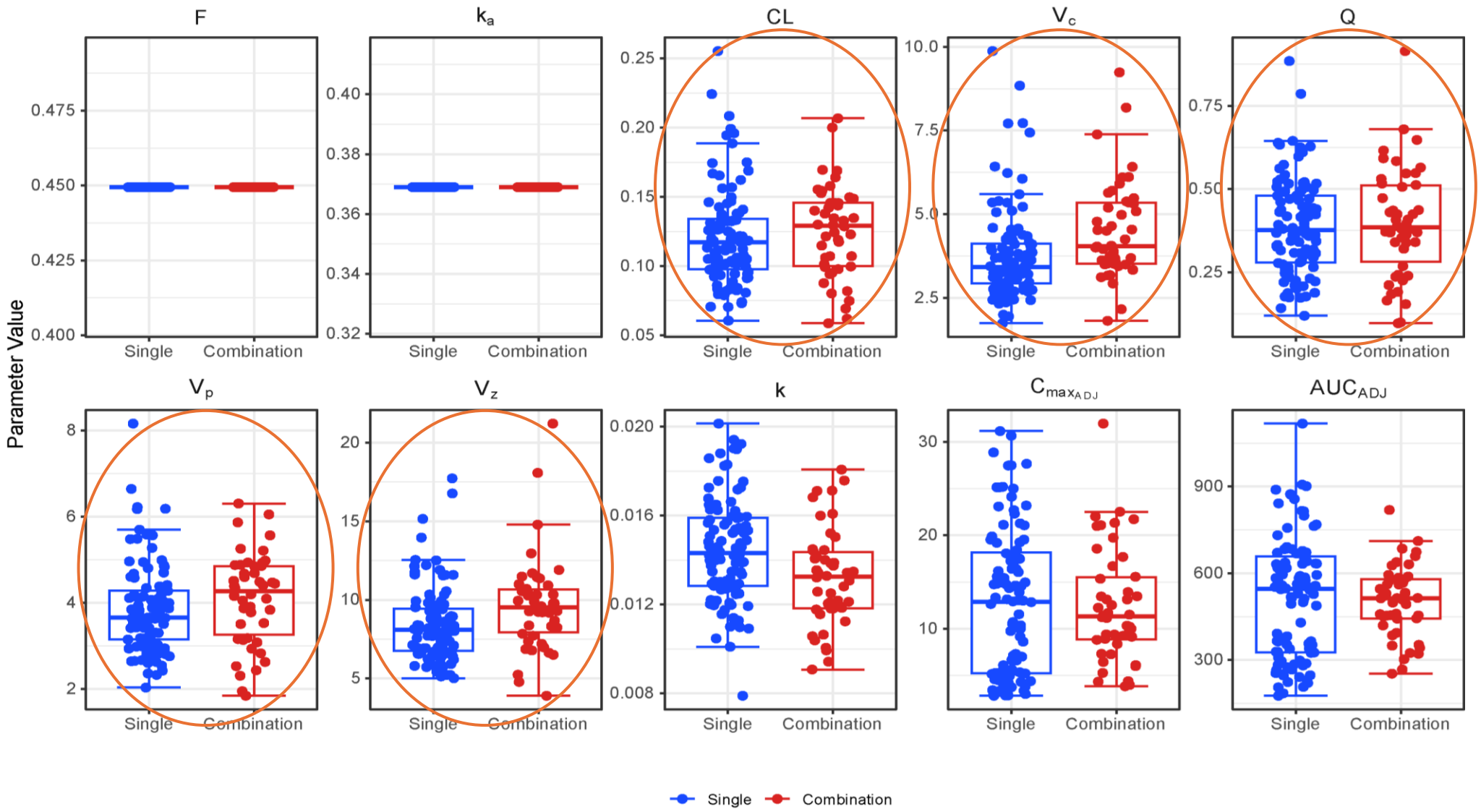

Study Cohort
Per-Protocol Primary Endpoint Cases
(n=146)
HVTN 127 / HPTN 087
n=100
HVTN 130 / HPTN 089
n=26
HVTN 136 / HPTN 092
n=20
VRC07-523LS
2.5 mg/kg IV
n=19
VRC07-523LS
5 mg/kg IV
n=19
VRC07-523LS
20 mg/kg IV
n=21
VRC07-523LS
2.5 mg/kg SC
n=21
VRC07-523LS
5 mg/kg SC
n=20
VRC07-523LS
+ PGT121
20 mg/kg IV
n=6
VRC07-523LS
+ PDGM1400
20 mg/kg IV
n=6
VRC07-523LS
+ 10-1074
20 mg/kg IV
n=5
VRC07-523LS
+ PGT121 + PDGM1400
20 mg/kg IV
n=9
VRC07-523LS
+ PGT121.414LS
20 mg/kg IV
n=10
VRC07-523LS
+ PGT121.414LS
5 mg/kg SC
n=10
Month 0, 4, 8, 12, and 16
Month 0 (double)
Month 0 and 4 (triple)
Month 0, 4, and 8

| Characteristic | Combination N = 46<br>[(n (%); median (range)] | Single N = 100<br>[(n (%); median (range)] |
|---|---|---|
| **Sex** | | |
| Female | 24 (52%) | 61 (61%) |
| Male | 22 (48%) | 39 (39%) |
| **Weight (kg)** | 71 (46, 109) | 76 (48, 114) |
| **Creatinine Clearance (mL/min)** | 120 (73, 183) | 122 (66, 220) |
| **Age (years)** | 28 (19, 50) | 28 (18, 50) |
| **Country of study** | | |
| United States | 46 (100%) | 92 (92%) |
| Switzerland | 0 (0%) | 8 (8%) |

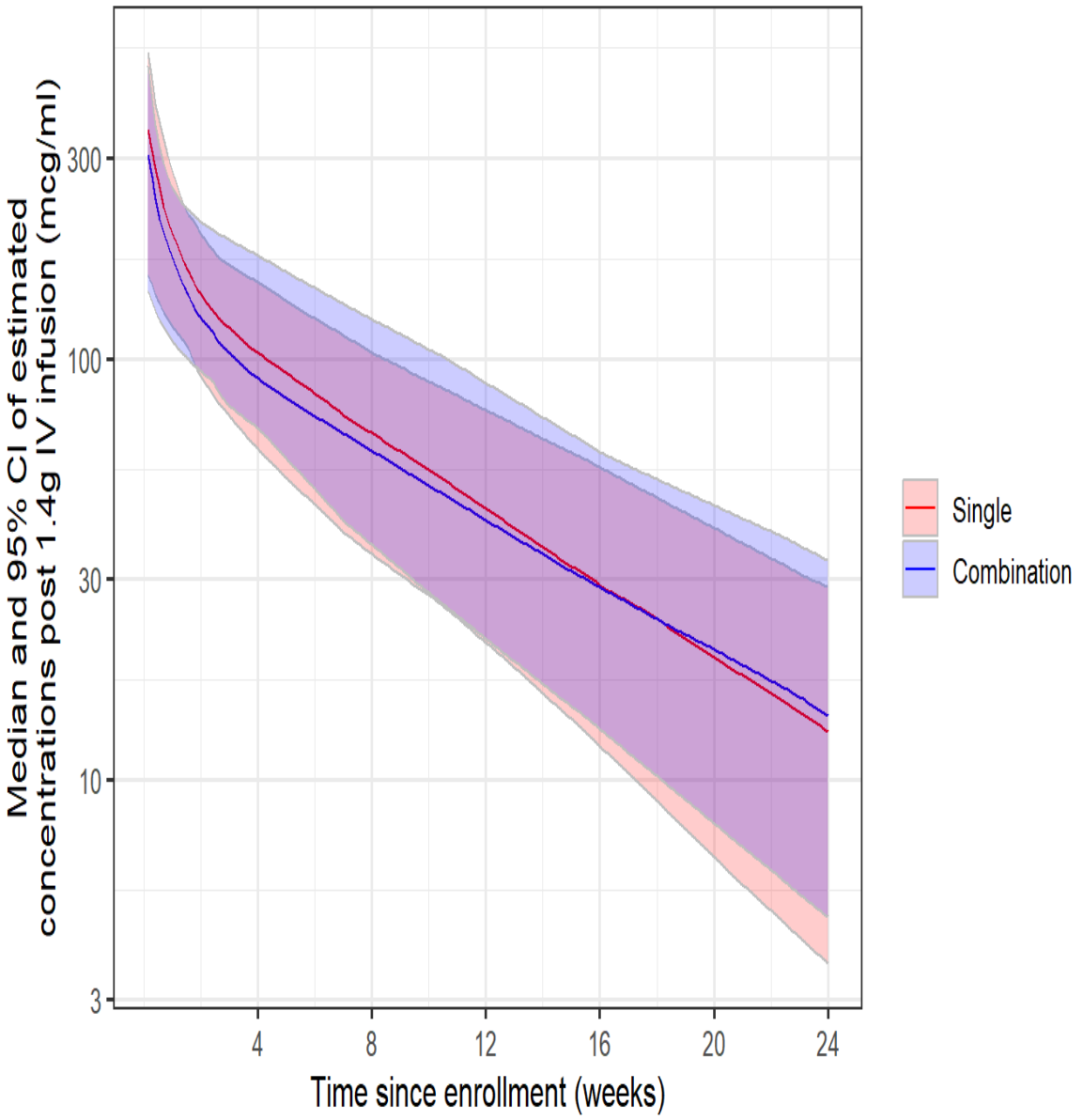

VRC07-523LS Concentration (µg/mL)
1000
500
100
50
10
1
0.1
≤0.05
0
28
56
84
112
140
168
224
280
336
392
448
504
560
616
672
728
784
840
Days
VRC07-523LS Dose
5 mg/kg
20 mg/kg
2.5 mg/kg
SPA
IV Single SPA
SC Single SPA
IV Combination SPA
SC Combination SPA


VRC07-523LS Concentration (μg/mL)
1000
100
10
1
≤ 0.05
0
200
400
600
800
Days
HVTN 127/HPTN 087 T1: VRC07-523LS 2.5 mg/kg Day(0, 112, 224, 336, 448)
HVTN 127/HPTN 087 T2: VRC07-523LS 5 mg/kg Day(0, 112, 224, 336, 448)
HVTN 127/HPTN 087 T3: VRC07-523LS 20 mg/kg Day(0, 112, 224, 336, 448)
HVTN 127/HPTN 087 T4: VRC07-523LS SC 2.5 mg/kg Day(0, 112, 224, 336, 448)
HVTN 127/HPTN 087 T5: VRC07-523LS SC 5 mg/kg Day(0, 112, 224, 336, 448)
HVTN 130/HPTN 089 T1: VRC07-523LS + PGT121 20 mg/kg Day 0
HVTN 130/HPTN 089 T2: VRC07-523LS + PGDM1400 20 mg/kg Day 0
HVTN 130/HPTN 089 T3: VRC07-523LS + 10-1074 20 mg/kg Day 0
HVTN 130/HPTN 089 T4: VRC07-523LS + PGT121 + PGDM1400 20 mg/kg Day(0, 112)
HVTN 136/HPTN 092 T5: VRC07-523LS + PGT121.414.LS 20 mg/kg Day(0, 112, 224)
HVTN 136/HPTN 092 T6: VRC07-523LS + PGT121.414.LS SC 5 mg/kg Day(0, 112, 224)

# VRC07-523LS PK parameters similar with combo and alone



# Similar concentration over time from combination and single administration VRC07-523LS




| Predicted concentrations at: | Single: Mean (95% CI) (N=100) | Combination: (95% CI) (N=46) | Combination/Single: Ratio (95% CI) | Two-sided raw p-value | Two-sided adjusted p-value |
|---|---|---|---|---|---|
| 1 day post 1.4g IV infusion (mcg/ml) | 332.68 (299.8, 369.17) | 271.34 (244.02, 301.71) | 0.82 (0.75, 0.88) | <0.001 | <0.001 |
| 4-Week post 1.4g IV infusion (mcg/ml) | 103.99 (98.15, 110.18) | 94.28 (89.34, 99.49) | 0.91 (0.86, 0.96) | <0.001 | 0.00 |
| 8-Week post 1.4g IV infusion (mcg/ml) | 66.73 (62.81, 70.89) | 61.75 (58.02, 65.71) | 0.93 (0.87, 0.99) | 0.02 | 0.09 |
| 16-Week post 1.4g IV infusion (mcg/ml) | 29.06 (26.96, 31.33) | 28.86 (26.78, 31.11 | 0.99 (0.91, 1.08) | 0.88 | 1.00 |

# Vc and Vp were higher in combination administration via the TMLE method

| PK Features | Description | Single: Mean (95% CI) (N=100) | Combination: (95% CI) (N=46) | Combination/Single: Ratio (95% CI) | Two-sided raw p-value | Two-sided adjusted p-value |
|---|---|---|---|---|---|---|
| **CL (L/day)** | Clearance from the central compartment | 0.12(0.11. 0.13) | 0.13 (0.12, 0.13) | 1.06 (1.00, 1.13) | 0.06 | 0.17 |
| **Vc (L)** | Volume of the central compartment | 3.74 (3.26, 4.29) | 4.66 (4.07, 5.34) | 1.25 (1.14, 1.37) | <0.001 | <0.001 |
| **Q (L/day)** | Inter-compartmental distribution clearance | 0.30 (0.22, 0.41) | 0.30 (0.22, 0.41) | 1.00 (0.91, 1.11) | 0.97 | 0.97 |
| **Vp (L)** | Volume of the peripheral compartment | 3.51 (3.07, 4.01) | 3.89 (3.45, 4.38) | 1.11 (1.04, 1.18) | <0.001 | 0.01 |

# Elimination half-life was higher in combination admin via the TMLE method

| PK Features | Description | Single: Mean (95% CI) (N=100) | Combination: (95% CI) (N=46) | Combination/Single: Ratio (95% CI) | Two-sided raw p-value | Two-sided adjusted p-value |
|---|---|---|---|---|---|---|
| **Distribution half-life (day)** | Length of time for serum concentration of the mAb to decrease by half in the distribution phase | 3.71 (2.75, 5.01) | 4.23 (3.15, 5.69) | 1.11 (1.05, 1.17) | 0.01 | 0.06 |
| **Elimination half-life (day)** | Length of time for serum concentration of the mAb to decrease by half in the elimination phase | 47.67 (45.46, 49.98) | 52.84 (50.17, 55.66) | 1.11 (1.05, 1.17) | <0.001 | 0.00 |
| **Dose normalized steady-state AUC (day/L)** | Dose-normalized area under the curve assuming a single IV administration | 8.42 (7.96, 8.9) | 7.94 (7.52, 8.39) | 0.94 (0.89, 1) | 0.06 | 0.17 |

# Discussion

- Most PK parameters did not differ significantly between combination and single groups
- Mean elimination half-life was slightly longer for combination vs. single administration
- Mean covariate-adjusted central volume of distribution (Vc) and peripheral volume of distribution (Vp) were slightly larger for combination vs. single administration, respectively
- Overall exposure/concentration over time was comparable between group

***These results support the design of combination bnAb trials***

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- Atlanta - Ponce de Leon
- Birmingham
- Boston - Brigham
- Boston - Fenway
- Chapel Hill
- Lausanne
- New York - Physicians & Surgeons

## HVTN 130/HPTN 089 sites:

- Boston – Fenway
- Nashville
- New York – Harlem Prevention
- New York – Physicians & Surgeons

## HVTN 136/HPTN 092 sites:

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- Chapel Hill
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- Philadelphia
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