SUMMARY OF RESULTS

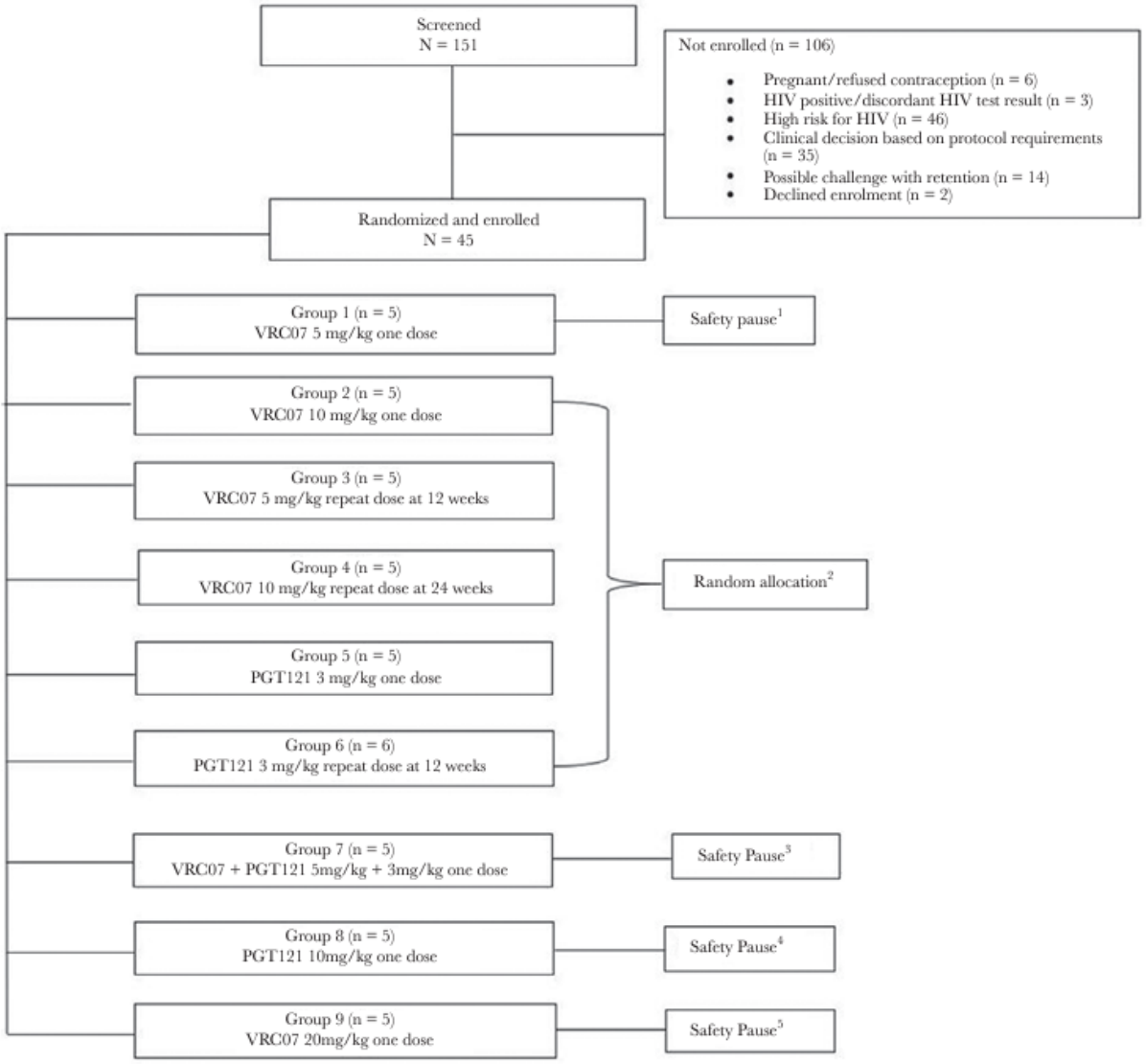
A Phase I Study to determine the Safety and Pharmacokinetics of the Human monoclonal Antibodies, VRC07-523LS and PGT121 administered subcutaneously to HIV negative Adults in South Africa (CAPRISA 012A)

PACTR201808919297244

Baseline Characteristics

A total of 151 participants were screened and 45 were enrolled into the trial. One hundred and four volunteers did not meet eligibility criteria and 2 decided not to enroll. Forty-four of the participants (98%) successfully completed the study, whereas 1 participant in Group 8 was lost to follow up after 58 weeks. Study participants were healthy women with a median age of 24 years.

Participant Flow (PRISMA)



Adverse Events

Product administrations were safe and well tolerated. All reported reactogenicity events were mild and resolved within the 3-day assessment period. There were no moderate or severe reactogenicity events reported. The most common events were injection site tenderness and headaches. A total of 161 AEs were reported. Of these, 9 were deemed related to study product and occurred within 7 days after product administration. These AEs included proteinuria in 7 participants: 4 received 5 mg/kg VRC07-523LS, 1 received 20 mg/ kg VRC07-523LS, 1 received 3 mg/kg PGT121, and 1 received placebo. There were also 2 separate AEs of elevated alanine aminotransferase and aspartate aminotransferase in 2 participants who received 3 mg/kg PGT121. All related AEs were mild in severity and resolved in a median of 7 days (interquartile range, 7–21). There was 1 reported unrelated serious AE of polytrauma due to a motor vehicle accident that occurred 50 days after study product administration.

- Total Adverse Events: 161
- Serious Adverse Events: 1 (polytrauma due to a motor vehicle accident, unrelated to the study product)
- Mild Reactogenicity Events: Injection site tenderness and headaches
- Moderate/Severe Reactogenicity Events: None
- AEs Related to Study Product: 9 (occurred within 7 days after product administration)
- Proteinuria: 7 participants (4 received 5 mg/kg VRC07-523LS, 1 received 20 mg/kg VRC07-523LS, 1 received 3 mg/kg PGT121, 1 received placebo)
- Elevated ALT and AST: 2 participants (both received 3 mg/kg PGT121)
- All related AEs were mild and resolved within a median of 7 days (IQR, 7-21 days)

Outcome Measures

<u>Primary Endpoints</u>

Safety and Tolerability of the Study Products:

- Measurement: Incidence of adverse events (AEs) and reactogenicity events.
- Result:
    - Product administrations were safe and well tolerated.
    - All reported reactogenicity events were mild and resolved within the 3-day assessment period.
    - No moderate or severe reactogenicity events were reported.
    - A total of 161 AEs were reported, with 9 related to the study product, all mild and resolving within a median of 7 days.

<u>Secondary Endpoints</u>

Pharmacokinetics of VRC07-523LS and PGT121:

- Measurement: Serum concentrations, C_{max}, T_{max}, $AUC_{0\text{-}12WK}$, and other pharmacokinetic parameters.
- Result:
    - VRC07-523LS concentrations increased nearly in proportion to dose at late time points.
    - The median observed VRC07-523LS concentrations after 5, 10, and 20 mg/kg doses were 5.83, 10.05, and 15.06 µg/mL at 12 weeks; 2.52, 3.78, and 9.65 µg/mL at 16 weeks; and 0.96, 1.35, and 3.86 µg/mL at 24 weeks.

- The median C_{max} after 5, 10, and 20 mg/kg doses were 42.14, 83.18, and 70.75 µg/ mL.
- The median T_{max} after 5, 10, and 20 mg/kg doses were 4.8, 2.8, and 2.8 days.
- The AUC for the first 12 weeks after 5, 10, and 20 mg/kg doses were 1474.2, 3194.9, and 2010.9 µg/mL
- Observed median PGT121 concentrations after 3 and 10 mg/ kg doses were 3.90 and 25.35 µg/mL at 4 weeks and below the limit of quantitation for the 3 mg/kg dose beyond 8 weeks.
- The PK modeling of 20 mg/kg VRC07-523LS showed that at 16 weeks the median concentration was 8.1 µg/mL, and 99.6% of concentrations were greater than 1 µg/mL, and 78% of concentrations greater than 5 µg/mL. At 24 weeks, the median concentration was 3.2 µg/mL, and 87% of concentrations were greater than 1 µg/mL, and 95% of concentrations were greater than 0.5 µg/mL.
- The PK modelling of 20 mg/kg PGT121 at 16 weeks showed a median concentration of 1.1 µg/mL and that 52% of concentrations were greater than 1 µg/mL and 66% of concentrations greater than 0.5 µg/mL. At 24 weeks, the median concentration was 0.13 µg/mL with 16% of concentrations greater than 1 µg/ mL and 26% greater than 0.5 µg/mL

Neutralizing Antibody Titers:

- Measurement: ID_{50} titers of VRC07-523LS and PGT121 against HIV.
- Result:
  - Potent neutralization observed from Day 1, peaking between Day 3 and 7.
  - High-dose groups had higher titers at peak, declining to similar levels as the lower dose groups at week 24.
  - Repeat dosing significantly increased neutralizing antibody titers, which then decreased to undetectable levels at 12 and 24 weeks after the second dose.
  - Serum virus neutralization titers were consistent with serum PK concentrations.

Acceptability of Subcutaneous Administration:

- Measurement: Participant satisfaction with the injection procedure and schedule.
- Result:
  - 100% of participants were satisfied with the explanation of the injection procedure.
  - 86.7% found the injection schedule of 2-3 injections per year acceptable.
  - 96% would recommend the injection to others if effective.
  - 91% would disclose receipt of the injection to their partners.

HIV Assay Cross-Reactivity:

- Measurement: Incidence of positive HIV enzyme immunoassay responses and cross-reactivity.
- Result:
  - No participant had a positive HIV enzyme immunoassay response.
  - No cases of cross-reactivity were observed with the two HIV rapid antibody testing kits.

Antidrug Antibody (ADA) Analysis:

- Measurement: Presence of antidrug antibodies.

- Result:
    - No ADA detected at any time point.
    - Participants showed no evidence of diminished peak or trough concentrations after repeat doses.

Reference

1.
Mahomed S, Garrett N, Capparelli EV, Osman F, Harkoo I, Yende-Zuma N, et al. Safety and Pharmacokinetics of Monoclonal Antibodies VRC07-523LS and PGT121 Administered Subcutaneously for Human Immunodeficiency Virus Prevention. The Journal of Infectious Diseases [Internet]. 2022 Aug 26 [cited 2023 May 22];226(3):510–20. Available from: https://pubmed.ncbi.nlm.nih.gov/35134995/