Project Brief: V114-030

Full Title of Study/Programme	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™23 Eight Weeks Later in Children Infected with Human Immunodeficiency Virus (HIV) (PNEU–WAY PED)
Technical Focus Area	Research Pediatric
Rationale	Human immunodeficiency virus (HIV) infection leads to defects in the humoral and cellmediated immune systems of infected children. These children are then at an increased risk for infection with various microbial agents, including Streptococcus pneumoniae [Janoff, E.N., et al 1992] [Janoff, E. N., et al 1993] [Bliss, S. J., et al 2008] [Madhi, S. A., et al 2000][Madhi, S. A., et al 2000]. The incidence of invasive pneumococcal disease (IPD) is estimated to be 9- to 43-fold higher in HIV infected children as compared with HIV uninfected children and this burden is more apparent in resource-poor settings [Madhi, S. A.,et al 2000] [Madhi, S. A., et al 2001] [Peters, V. B., et al 1994] [Spector, S. A., et al 1994][Dankner, W. M., et al 2001] [Andiman, W. A., et al 1996] [Jones, N., et al 1998] [Nachman,S., et al 2005] [Laufer, M. K., et al 2006]. Routine PCV immunization of children is effective in preventing vaccine serotype-specific pneumococcal disease, including in HIV infected children, where it has been shown to decrease the risk of IPD [Centers for Disease Control and Prevention 2005] [Whitney, C. G.,et al 2003]. Given the high morbidity and mortality associated with IPD, immunization guidelines recommend that children and adolescents infected with HIV who have not been vaccinated with the 13-valent Prevnar 13™ vaccine, receive a catch-up dose of Prevnar 13™. These guidelines also recommend that children infected with HIV receive the 23-valent pneumococcal polysaccharide (PnPs) vaccine, PNEUMOVAX™23, at least 8 weeks after receiving PCV, followed by another dose of PNEUMOVAX™23 not less than 5 years later [Bliss, S. J., et al 2008] [Robinson, C. L., et al 2018] [Centers for Disease Control and Prevention (CDC) 2013] [National Center for Immunization and Respiratory Diseases 2018]. Despite the commercial availability of pneumococcal vaccines, pneumococcal disease remains an important worldwide concern due to lack of universal availability of

	vaccines and due to the emergence of non-vaccine serotypes. V114 contains all the pneumococcal serotypes contained in Prevnar 13™ plus 2 additional serotypes (22F, 33F), which have emerged as important causes of IPD. This clinical study is designed to evaluate the safety, tolerability, and immunogenicity of V114 in children (6 to 17 years of age inclusive) infected with HIV (CD4+ T-cell count ≥200 cells/µL and a plasma HIV ribonucleic acid [RNA] value <50,000 copies/mL tested at Screening). In comparison to Prevnar 13™, V114 has the potential to provide comparable protection against pneumococcal disease caused by the serotypes in common between the 2 vaccines and offer additional protection against IPD caused by the 2 PnPs serotypes (22F and 33F) not contained in Prevnar 13™.
Primary Objectives	• To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs). • To evaluate the anti-pneumococcal polysaccharide (PnPs)serotype-specific Immunoglobulin G (IgG)Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) with V114 or Prevnar 13™ by each vaccination group.
Secondary Objectives	• To evaluate the safety and tolerability of PNEUMOVAX™23 administered 8 weeks following V114 with respect to the proportion of participants with AEs. • To evaluate the anti-PnPs serotype-specific opsonophagocytic activity(OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination (Day 30) with V114 or Prevnar 13™ by each vaccination group • To evaluate the anti-PnPs serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PNEUMOVAX™23 (Week 12) by each vaccination group.
Primary Endpoint/Outcome	Following vaccination with V114: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination • Vaccine-related serious adverse events (SAEs) through completion of study participation • Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at Day 30
Secondary Endpoint/Outcome	Following vaccination with PNEUMOVAX™23: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination

	• Solicited systemic AEs from Day 1 through Day 14 postvaccination • Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at Day 30 • Anti-PnPs Serotype-specific OPA and IgG responses for the 15 serotypes contained in V114 at Week 12
Study Design	This is a randomized, active comparator-controlled, parallel-group, multi-site, double-blind (with in-house blinding), study of V114 in participants 6 to 17 years of age inclusive infected with HIV. Approximately 400 participants will be randomly assigned in a 1:1 ratio to receive either V114 or Prevnar 13™ on Visit 2 (Day 1). Randomization will be stratified by CD4+ T-cell count as follows: • Stratum 1: CD4+ T-cell count ≥200 to <500 cells/μL. • Stratum 2: CD4+ T-cell count ≥500 cells/μL. Approximately 20% or more of the participants will be enrolled into Stratum 1. All participants will also receive a single dose of PNEUMOVAX™23 at Visit 4 (Week 8). Participants will be followed for injection-site and systemic AEs through Day 14 following each vaccination. Information for SAEs and deaths, regardless of whether the events are considered to be vaccine-related by the investigator, will be collected from the time consent is signed through completion of participation in the study. An external Data Monitoring Committee (DMC) will conduct a periodic review of safety and tolerability data for the V114 Phase 3 pediatric program. A description of the structure and function of the DMC, along with the timing and content of the safety reviews will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1. Blood samples for immunogenicity assays will be drawn immediately before V114 or Prevnar 13™ vaccination at Visit 2 (Day 1), at 30 days postvaccination at Visit 3 (Day 30), and 30 days after PNEUMOVAX™23 vaccination at Visit 5 (Week 12). After completion of immunogenicity testing to evaluate the study objectives, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. For randomized study participants who provided consent/assent for future biomedical research, leftover sera from the study may be used for other purposes such as the development and/or validation of pneumococcal assays after completion of all study related immunogenicity testing.

Study Arms	
Study Population	HIV infected children 6 to 17 years of age inclusive
Study Sample Size	400 participants
Follow-up/Duration	19 months from the time the first participant signs the informed consent/assent until the last participant's last study-related telephone call or visit
Study/Programme Sites	Wits RHI Shandukani Research Centre (SRC
Study/Programme Duration	Start Date: Dec 2019 Estimated End Date: Apr 2021
Intervention	There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive V114 and PNEUMOVAX™23 or Prevnar 13™ and PNEUMOVAX™23.
Operations	Study Specific
Investigators	• Dr Faeezah Patel, Principal Investigator • Dr Masebole Masenya • Dr Elizea Horne • Prof Lee Fairlie
Other Partners & Collaborators	
Sponsors/Donors	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (hereafter referred to as the Sponsor or MSD)
Publications/Key Presentations to Date	None as yet
Progress Update as at Jul 2020	Screened: 30 Enrolled:29
Frequency of Donor Narrative Report	Monthly
Overall Study/Project Contact	Dr Hermien Gous (hgous@wrhi.ac.za)
Briefing Owner and Date	