Title Page

Protocol Title: A randomized, placebo-controlled, observer-blind, phase 2 study to evaluate safety and immunogenicity of the investigational M72/AS01$_E$ *Mycobacterium tuberculosis* (*Mtb*) vaccine in virally suppressed, antiretroviral-treated participants with human immunodeficiency virus (HIV)

Protocol Number: Gates MRI TBV02-202

Study Phase: Phase 2

Short Title: Safety and immunogenicity of a *Mycobacterium tuberculosis* vaccine M72/AS01$_E$ in participants with well-controlled HIV

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	anti-retroviral therapy
AST	aspartate aminotransferase
BARC SA	Bio Analytical Research Corporation, Republic of South Africa
βHCG	beta human chorionic gonadotropin
BCG	Bacille Calmette-Guerin
CD	cluster of differentiation
CFR	Code of Federal Regulations
CoP	correlate of protection
CoR	correlate of risk
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
EDC	electronic data capture
GCP	Good Clinical Practices
GMC	geometric mean concentration
HIV	human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IL	interleukin
IM	Intramuscular(ly)
IRB	Institutional Review Board
IRIS	immune reconstitution inflammatory syndrome
IVRS	interactive voice response system
IWRS	interactive web response system
LAR	legally acceptable representative
M72/AS01$_E$	candidate (experimental) TB vaccine
mL	milliliter
µL	microliter
Mtb	*Mycobacterium tuberculosis*
NA	not applicable
OI	opportunistic infection
PBMC	peripheral blood mononuclear cells
PI	Principal investigator
pIMD	potential immune-mediated disease

PPD	purified protein derivative
QFT assay	QuantiFERON®-TB Gold Plus assay
RNA	ribonucleic acid
RSA	Republic of South Africa
SAE	serious adverse event
SAHPRA	(Republic of) South African Health Products Regulatory Authority
SAP	statistical analysis plan
SoA	schedule of activities
SUSAR	serious, unexpected, suspected adverse drug reactions
TB	tuberculosis
TNF	tumor necrosis factor
TPT	TB preventive therapy
WBC	white blood cell
WHO	World Health Organization

1. Protocol Summary

1.1. Synopsis

Protocol Title: A randomized, placebo-controlled, observer-blind, phase 2 study to evaluate safety and immunogenicity of the investigational M72/AS01$_E$ *Mycobacterium tuberculosis* (*Mtb*) vaccine in virally suppressed, antiretroviral-treated participants with human immunodeficiency virus (HIV)

Short Title: Safety and immunogenicity of a TB vaccine M72/AS01$_E$ in participants with well-controlled HIV

Rationale:
Published phase 1 and 2 randomized, controlled trials evaluating M72/AS01$_E$ vaccination in individuals with HIV who were receiving antiretroviral therapy (ART) show that a 2-dose schedule of the vaccine given one month apart is well-tolerated and immunogenic in this population. This current study intends to confirm that the vaccine is safe, well-tolerated, and immunogenic in a larger population of people with virally suppressed HIV infection in a tuberculosis (TB) endemic region.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of M72/AS01$_E$ vaccination	• Solicited adverse events (AEs) through 7 days post each dose of study intervention • Unsolicited AEs through 28 days post each dose of study intervention • All serious adverse events (SAEs) through end of study
Secondary	
• To assess the safety of M72/AS01$_E$ vaccination	• Potential immune-mediated diseases (pIMDs) through end of study • Safety laboratory assessments grade 3 or above through end of study
• To assess the humoral immunogenicity of M72/AS01$_E$ vaccination	• M72-specific antibody titers at Day 1, Day 29, Day 57, Day 210 and Day 390
• To assess the cellular immunogenicity of M72/AS01$_E$ vaccination	• Frequency and magnitude of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by expression of IFN-γ or IL-2 using intracellular cytokine staining (ICS) at Day 1, Day 57 and Day 390
Exploratory	
• To further explore cellular immunogenicity of M72/AS01$_E$ vaccination	• Frequency and magnitude of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by expression of IFN-γ or IL-2 by ICS at Day 29 and Day 210 • Polyfunctionality of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by co-expression of multiple functional markers by ICS
• To assess HIV viral load post-M72/AS01$_E$ vaccination	• Frequencies of participants with confirmed HIV ribonucleic acid ([RNA]>200 copies/mL) at Day 57, Day 210 and Day 390
• To assess changes in CD4$^+$ T cell count from baseline	• Mean changes in CD4$^+$ T cell count from baseline to Day 57, Day 210 and Day 390

Objectives	Endpoints
• To describe the incidence of suspected TB disease and laboratory-confirmed pulmonary TB disease	• Suspected TB during the study • Laboratory-confirmed pulmonary TB during the study
Other exploratory endpoints may include, but are not limited to, assessing functional antibody profiles in response to vaccination, vaccine-induced changes in innate and myeloid cell populations, and vaccine-induced changes in transcriptomic, proteomic or metabolomic profiles.	

CD= cluster of differentiation

Overall Design

Disclosure statement: This is randomized, observer-blind, placebo-controlled, clinical trial of M72/AS01$_E$ tuberculosis vaccine vs. placebo in approximately 400 males and females between 16 to 35 years of age inclusive, who are living with HIV infection, and are virally suppressed (i.e., viral load < 200 copies per mL) on ART.

Interventional model: Participants will be randomly assigned 1:1, to one of two groups in parallel for the duration of the study.

Intervention groups: 2 study groups (M72/AS01$_E$ group and placebo group), will each receive 2 vaccinations administered intramuscularly (IM) in the deltoid muscle, preferably of the non-dominant arm, one month apart (at Day 1 and Day 29).

- M72/AS01$_E$ group: A 0.5 mL dose of M72/AS01$_E$ contains 10µg M72 reconstituted with AS01$_E$, a GSK proprietary adjuvant system containing 25 µg MPL (3-O-desacyl-4-monophosphoryl lipid A produced by GSK), 25 µg QS-21 (*Quillaja saponaria* Molina, fraction 21). The vaccine will be administered at Day 1 and Day 29.
- Placebo group: Each dose contains 0.5 mL saline (0.9% NaCl). The placebo will be administered at Day 1 and Day 29.

Primary purpose: To assess the safety as well as immunogenicity of M72/AS01$_E$ vaccine in participants with virally suppressed HIV infection on ART

Safety and immunogenicity outcomes will be followed for 12 months after the second vaccination (end of study) for each randomized participant.

Masking: The study is observer-blind: participants, sponsor, contract research organization (CRO) clinical team, laboratory, investigators and site staff will be blinded to the randomization. An Independent Data Monitoring Committee (IDMC) will review unblinded data. The investigational pharmacist preparing study interventions will be unblinded but will not perform other study duties.

Safety Monitoring: An IDMC will be established to oversee the safety of this study. The IDMC will review unblinded safety data during regular scheduled safety review meetings, and may request additional information, or a pause in recruitment and vaccination, while safety data are being evaluated.

Number of participants: Approximately 400 participants will be enrolled.

Randomization: Participants will be randomized 1:1, stratified by site, and QuantiFERON-TB Gold Plus (QFT) status, based on results at screening.

Adverse events of special interest (AESIs): Protocol-defined potential immune-mediated diseases will be assessed throughout the study.

Analysis: The final analysis will occur after all participants have reached the end of the study (Day 390).

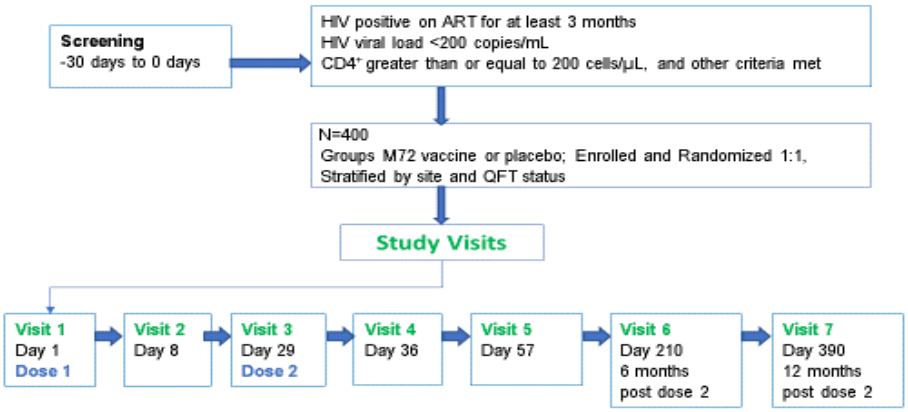
Total duration of study participation: The study duration for each participant, after screening, is approximately 390 days, which includes, 2 vaccinations 1 month apart, and 365 days of follow-up post dose 2. Enrollment is expected to take approximately 6 months.

Study sites: Approximately 6 sites in the Republic of South Africa (RSA) will participate in this study.

Schema: The screening visit will begin with the informed consent process.

Approximately 400 study-eligible participants will be randomized 1:1 to receive M72/AS01$_E$ vaccine or placebo IM. Study procedures are outlined in Figure 1 (Schema) and Table 2 (Schedule of activities).

Figure 1: Study Schema



1.2. Schedule of Activities

Written informed consent must be given before any screening procedure is started. Each enrolled participant will have seven clinic visits after screening. Study procedures are summarized in the Schedule of Activities (SoA) in Synopsis Table 2.

Table 2: Schedule of Activities (SoA)

Procedure	Screen	Intervention and Follow-up Period							
		Visit 1 Day 1	Visit 2 Day 8	Visit 3 Day 29	Visit 4 Day 36	Visit 5 Day 57	Visit 6 Day 210	Visit 7 Day 390	Discon Visit
Visit window	-30 to Day 0	±0	Day 8 to 12	Day 29 to 35	Day 36 to 42	Day 57 to 63	±28days	±28days	
Informed consent/assent	X								
Inclusion and exclusion criteria-verify eligibility	X	X							
Full medical history/full physical examination (PE), height	X								
Record Body weight, and pregnancy status	X	X	X	X	X	X	X	X	X
Focused medical history/focused PE		X	X	X	X	X	X	X	X
Vital signs	X	X		X					
βHCG serum pregnancy test (5mL)	X	X		X		X	X	X	X
Randomization		X							
Hepatitis B and C screening (3 mL)	X								
Urine pregnancy test (prior to study intervention administration)		X		X					
Safety laboratory assessments (7 mL)	X	X		X					X
Urinalysis by dipstick (glucose, protein, blood), and microscopy	X								
HIV antibody assessment (10 mL)	X								
HIV viral load assessment (3 mL)	X	X				X	X	X	X
$CD4^+$ cell count (3 mL)	X	X				X	X	X	X
QFT assay (4 mL)	X							X	X
Sputum Xpert MTB/RIF assay	X								
Sputum Xpert MTB/RIF assay ONLY if TB is suspected		X	X	X	X	X	X	X	X
Study Intervention Administration		X		X					
30- minute post admin. observation		X		X					
Diary card training and distribution		X		X					
Diary card: return, review, transcribe			X		X				
Memory aid training and distribution (unsol. AEs/ conmeds)			X		X				
Memory aid: return, review, transcribe				X		X			
Record AE (at screening until Day 1)	X								
Record solicited AEs		X	X	X	X				
Record unsolicited AEs		X	X	X	X	X			X
Record all SAEs and AESIs	X	X	X	X	X	X	X	X	X
Record concomitant medications		X	X	X	X	X	X	X	X

Procedure	Screen	Intervention and Follow-up Period							
		Visit 1 Day 1	Visit 2 Day 8	Visit 3 Day 29	Visit 4 Day 36	Visit 5 Day 57	Visit 6 Day 210	Visit 7 Day 390	Discon Visit
M72-specific IgG antibody (serum) (10mL)		X		X		X	X	X	X
M72-specific $CD4^+$ and $CD8^+$ T cells (17 mL)		X		X		X	X	X	X
Exploratory PBMC and plasma for CoP & CoR (34 mL)		X			X		X	X	X
Exploratory CoP & CoR serum(10 mL) innate and adaptive		X			X		X	X	X
Exploratory CoP & CoR transcriptomics (2.5 mL)		X			X		X	X	X

X indicates procedure to be performed and mL indicates blood volume collected (volumes listed are approximate)

Unsol. AE= unsolicited adverse event, conmed= concomitant medication

QFT= QuantiFERON®-TB Gold Plus assay (note that participants with an indeterminate result will not be eligible).

A discontinuation (discon) visit will be scheduled for participants who discontinue or withdraw, whenever possible. Any AEs will be collected.

As part of history/physical at each visit, a TB symptom/sign checklist and history of TB household contact will be included.

A single self-expectorated sputum sample will be collected for Xpert MTB/RIF assay from all participants at screening visit, and in participants with suspected TB at the other visits. No sputum induction is required. Sputum Xpert MTB/RIF assay will not be done in participants who are unable to produce sputum.

CoP and CoR= correlate of protection and correlate of risk

Note that all blood samples collected on Days 1 and 29 will be collected prior to study intervention administration.

Laboratory test results of samples collected at screening visit will be utilized to determine eligibility.

Laboratory test results of blood samples collected on Day 1 will be used to establish baseline pre-vaccination values (and not to determine eligibility), and blood samples collected at Day 29 will be used to establish baseline values prior to the administration of the second dose (and not to determine eligibility for second dose administration).

All blood volumes are approximate. Total amount of whole blood to be collected is approximately 423 mL (assuming all samples are collected at each visit and not at discon visit). Maximum amount of whole blood to be collected at any given visit is approximately 91.5 mL.

Note that the sponsor will evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment such as local labs and home visits) could be implemented when necessary and feasible, and would be sufficient to assure the safety of trial participants. Refer to Section 7.5 for details.

2. Introduction

Worldwide, TB is one of the top 10 causes of death, and the leading cause from a single infectious agent (above HIV/ acquired immunodeficiency syndrome [AIDS]). An estimated 10 million people became ill with TB in 2018, and an estimated 1.5 million people died from the infection, including 251,000 people also infected with HIV (WHO, 2019a).

Seven countries accounted for 64% of the new TB cases in 2016 including India, Indonesia, China, Philippines, Pakistan, Nigeria, and the Republic of South Africa (RSA). In 2016, in the WHO African region, where this current study will be conducted, 2.5 million people became ill with TB and an estimated 417,000 people died from the disease (among 1.7 million globally), accounting for approximately 25% of TB deaths worldwide (WHO, 2019b).

In endemic settings, HIV coinfection is the most important risk factor for developing active TB disease, which increases both the susceptibility to primary infection or reinfection, and the risk of TB reactivation for patients with latent TB. TB also has a negative impact on the immune response to HIV, accelerating the progression from HIV infection to AIDS (Bruchfeld, 2015).

TB is a leading cause of death among individuals with HIV. In 2016, 40% of HIV deaths globally, were due to TB. Among those living with HIV infection, the risk of developing TB was estimated to be between 16-27 times greater than among those without HIV infection. In 2015, almost 60% of TB cases among people living with HIV were not diagnosed or treated, resulting in 390,000 TB-related deaths among this population (WHO, 2019c).

The World Health Organization 'End TB strategy' calls for a global end to TB by 2035 using strategies such as early diagnosis, treatment, and prevention, including vaccination (WHO, 2019d). Towards that same end, the RSA, with one of the highest per capita rates of TB, implemented a plan in 2012 (National Strategic Plan or NSP) to control the spread of TB.

The Bacille Calmette–Guerin (BCG) vaccine is currently the only available TB vaccine but among several drawbacks, it is contra-indicated in people living with HIV except for special populations (e.g., newborns). HIV negatively impacts T-cell function, polarization and differentiation of *Mtb*-specific T cells, *Mtb* antigen presentation by dendritic cells, as well as B-cell and antibody-response (Nemes, 2018).

ART is the most effective preventive strategy against TB in people living with HIV, substantially reducing the risk irrespective of baseline $CD4^+$ cell count, tuberculin skin test status, and antimycobacterial drug resistance. Even so, ART alone is not expected to control HIV-associated TB, since it is often started late during HIV progression and many patients already have Mtb infection before starting ART. Even during long-term ART, TB incidence in the RSA is still higher than among people not infected with HIV (Lawn, 2015).

However, an effective TB vaccine that could provide adequate immunity against TB among immunocompromised individuals, including those who are living with HIV is possible. The GlaxoSmithKline (GSK) M72/AS01$_E$ (10 µg formulation) is a candidate vaccine to prevent TB disease that has shown promising results in phase 2 studies.

2.1. Background

The M72/AS01$_E$ vaccine contains the M72 recombinant fusion protein derived from two immunogenic *M. tuberculosis* antigens (*Mtb*32A and *Mtb*39A), 10 µg per dose, combined with GSK's AS01$_E$ adjuvant system. The *Mtb*39A and *Mtb*32A components of the recombinant antigen elicited specific lymphoproliferation, interferon-γ production, or both, in those with latent *Mtb* infection and active TB. To date, approximately 2300 participants have received the M72/AS01$_E$ vaccine (at least 4400 doses administered).

Two of these studies (TB-011 and TB-014) were conducted in adults living with HIV who have had no past or current TB disease. A total of 102 persons living with HIV were exposed to M72/AS01$_E$, and of these, 62 were virally suppressed on ART.

TB-011 was a phase I/II double-blind, randomized study in Switzerland (Thacher, 2014). All 37 participants had to be on ART for at least 6 months with viral load < 50 copies/mL and CD4$^+$ > 200 cells/µL. Thirty-seven were enrolled and randomized 3:1:1 to either M72/AS01$_E$ (n=22), AS01$_E$ alone (n=8) or saline (n=7). Vaccines were administered at Day 0 and Day 30. Follow up continued for 6 months post-second vaccination.

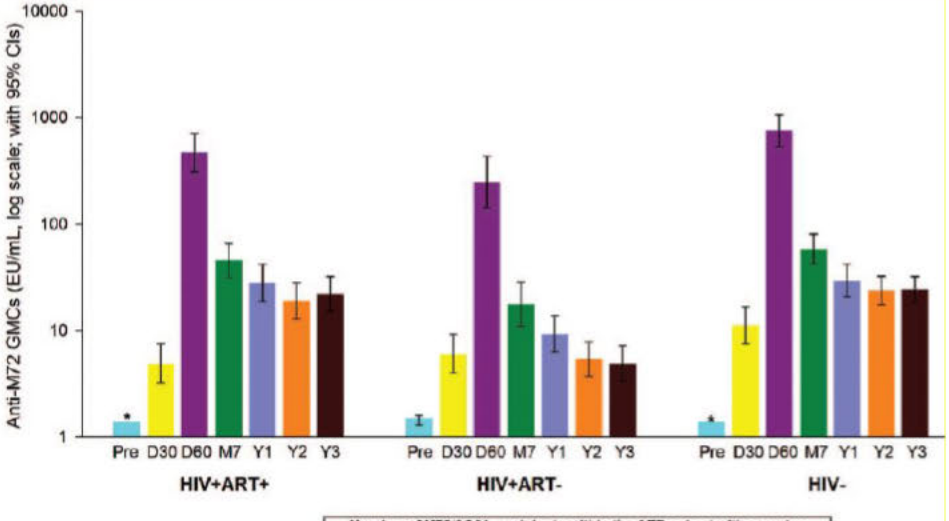
- Demographics and baseline: mean age 40 years old, 30% female, 78% Caucasian, 73% BCG+, 2.7% QFT+, mean purified protein derivative (PPD) skin test induration ≤5mm, CD4$^+$ 605 cells/µL, nadir CD4$^+$ 191 cells/µL.
- Safety and reactogenicity: No vaccine-related SAEs or study discontinuation due to an AE; 90% M72/AS01$_E$ participants reported pain at injection site, and about half reported fatigue and/or headache. Most AEs were mild or moderate in severity with infrequent grade 3 solicited AEs (local after ≤9.1% and general after ≤7.1% of doses). Five of 22 M72/AS01$_E$ participants had a transient CD4 decline of >100 cells/µL one-month post first injection that was deemed clinically insignificant. Their CD4$^+$ count remained above 200 cells/µL.
- Three participants had a single viral load blip that was clinically insignificant (i.e., 121 copies/mL at Day 30, and 55 and 59 copies/mL at Day 60).
- Immune response: Most had vaccine-induced response of M72-specific CD4$^+$ T cells expressing at least two markers among CD40L, interleukin (IL)-2, tumor necrosis factor (TNF)-α and interferon gamma (IFN-γ) by intracellular cytokine staining ([ICS] 89% at Day 60 and 91% at Day 210). These responses did not differ by BCG vaccination status. There was no correlation between CD4$^+$ cell counts and M72-specific CD4$^+$ T cell responses. Pre-existing responses at baseline were infrequent.
- All individuals were anti-M72 seronegative before vaccination. Geometric mean concentrations (GMCs) in the M72/AS01$_E$ group was highest at Day 60 and persisted at Day 210. All were seropositive after the second dose (Day 60) and remained so at Day 210.

TB-014 study was a phase II double-blind, randomized study in Chennai, India (Kumarasamy, 2016, Kumarasamy, 2018). A total of 240 participants were enrolled, 80 in each of 3 groups (HIV-uninfected controls, HIV+ on stable ART, and HIV+ ART-naïve). The ART-stable group had been on ART for at least 6 months and had CD4$^+$ ≥ 250 cells/µL and viral load < 400 copies/mL. The ART-naïve group were not yet eligible for ART according to standard of care, and had CD4$^+$ > 350 cells/ µL and viral load 5000-80,000 copies/mL. Each group was

randomized 1:1 to M72/AS01$_E$ vs. saline. Vaccines were administered at Day 0 and Day 30. The study duration was 13 months (1-year post dose 2) with a long term follow up phase to Year 3.

- Demographics and baseline: Among the M72/AS01$_E$-exposed participants with and without HIV (n=120): mean age 34.2 years, 32.5% female, 96.7% central/south Asian, 70.8% BCG+, 43.3% QFT+. Among ART-stable M72/AS01$_E$ participants: baseline viral load 150 copies/mL and CD4$^+$ 613 cells/µL, and nadir CD4$^+$ 219 cells/µL. Among ART-naïve M72/AS01$_E$ participants: baseline viral load 29,007 copies/mL, CD4$^+$ 517 cells/µL, and naïve CD4$^+$ 476 cells/µL.
- Safety and reactogenicity: Pain at injection site, fatigue and headache were the most common solicited AEs among M72/AS01$_E$ recipients, and were mostly mild or moderate in severity. Grade 3 pain was infrequent (≤7.6% of doses). Across all groups, the frequency of swelling of any intensity after all doses was ≤8.9% of doses, and no grade 3 swelling was reported. The only grade 3 general solicited AEs were headache in one ART stable participant and gastrointestinal symptoms in one HIV-negative participant. There were no significant differences in general solicited AEs between the HIV-negative, and the ART stable and ART-naïve HIV+ groups except more frequent fever and headaches were observed in the HIV-negative group.
- Unsolicited AEs reporting was comparable between the M72/AS01$_E$ vs. placebo groups within each cohort. These AEs tended to be higher in ART-naïve cohort, followed by ART-stable cohort and then the HIV-negative cohort. Most frequently reported AEs were nasopharyngitis, back pain, headache, cough, decreased appetite and pruritus. No grade 3 unsolicited AEs were reported.
- CD4 count and viral load were comparable between the M72/AS01$_E$ vaccine vs. placebo recipients with each cohort.
- Immune response: Several participants had pre-existing M72-specific CD4$^+$ T cell response by ICS (CD4$^+$ expressing at least two markers among CD40L, IL-2, TNF-α and IFN-γ). Vaccine induced responses were highest at Day 37 and persisted to Year 3. Vaccine-induced responses in the ART stable group were significantly higher than the ART-naïve groups from Day 30 onwards, but comparable to the HIV-negative group, from Day 60 onwards. Degree of polyfunctionality of the responding CD4$^+$ T cells tended to be higher in the QFT+ participants at Day 7 and Day 30, but was comparable to QFT- participants at subsequent time points. No M72-specific CD8$^+$ T cell responses were observed.
- Anti-M72 IgG responses peaked at Day 60 in the M72/AS01$_E$ group and persisted to year 3. The ART stable group had higher vaccine-induced IgG responses than the ART-naïve cohort but comparable to that of the HIV-negative cohort (Figure 2). The seropositivity rates at year 3 were 97.1% in ART stable, 66.7% in ART-naïve and 97.3% in HIV-negative cohorts.

Figure 2: Geometric mean concentrations of antibodies against M72



	Number of M72/AS01$_E$ recipients within the ATP cohort with samples available at each timepoint						
	Pre	D30	D60	M7	Y1	Y2	Y3
HIV+ART+	39	36	37	35	31	35	34
HIV+ART-	39	39	38	33	36	35	33
HIV-	39	38	36	37	28	35	37

(Kumarasamy, 2018)

In summary, these studies demonstrated that the M72/AS01$_E$ vaccine was immunogenic and well tolerated in people living with HIV. Irrespective of ART status, they mounted cell-mediated, and humoral responses to two M72/AS01$_E$ doses, which persisted up to 3 years post-dose 2 vaccination (Kumarasamy, 2018). M72/AS01$_E$ was well tolerated, immunogenic, and did not negatively affect the HIV-1 viral loads, $CD4^+$ T-cell counts, or ART regimens of the participants (Kumarasamy, 2016; Thacher, 2014).

2.2. Study Rationale

The randomized, controlled trials evaluating M72/AS01$_E$ vaccination in individuals living with HIV who were receiving ART (described in Section 2.1) showed that a 2-dose schedule of the vaccine given one month apart was well-tolerated and immunogenic in this population.

To date, there have been at least 102 individuals with HIV exposed to M72/AS01$_E$ in two studies (Kumarasamy, 2016; Kumarasamy, 2018; Thacher, 2014). This current study intends to confirm that the vaccine is safe, well-tolerated, and immunogenic in a larger population of people with virally suppressed HIV infection in a TB endemic region.

2.3. Benefit/Risk Assessment

Benefits to M72/AS01$_E$ vaccination are unknown at this time.

The following risk and benefit evaluation is focused on an HIV-positive population that received the M72/AS01$_E$ vaccine, based on published studies in India (Kumarasamy, 2016; Kumarasamy, 2018) and Switzerland (Thacher, 2014).

Solicited local AEs: The safety risks of study participation include a local reaction to the injections. In both studies, injection-site pain was the most commonly reported solicited local AE

in all cohorts. In the TB-014 Indian study, irrespective of cohorts, after all doses, grade 3 pain was reported infrequently and only in the M72/AS01$_E$ groups (≤7.6% of doses). Across groups and cohorts, the frequency of swelling (any intensity) after all doses was low (≤8.9% of doses) and no grade 3 swelling was reported. In the TB-011 Swiss study, grade 3 solicited local AEs were also infrequent, occurring after ≤9.1% of doses, and reported predominantly after M72/AS01$_E$.

Solicited general AEs: In both studies, headache and fever were the most frequently reported solicited general AEs across groups. In the India study, the only grade-3 general AEs were headache and gastrointestinal symptoms, reported in the ART-stable and HIV-negative cohorts, respectively (1 participant each, Kumarasamy, 2016). In the Swiss study, grade 3 solicited local and general AEs were also infrequent (occurring after ≤7.1% of doses) and reported predominantly after vaccination with M72/AS01$_E$ (Thacher, 2014).

Unsolicited AEs: In the Indian study, the incidence of unsolicited AEs was generally comparable between the vaccine and placebo groups, and tended to be highest in the ART-naive cohort, followed by the ART stable cohort and then the HIV-negative cohort. Nasopharyngitis, back pain, headache, cough, decreased appetite, and pruritus were most frequently reported, without clear patterns between groups, and were all considered not clinically significant. No grade 3 unsolicited symptoms were reported. Vaccine-related unsolicited AEs (injection-site induration among ART-stable participants; one participant per AE) were rare in the vaccine group and not reported in the placebo group (Kumarasamy, 2016).

Participants in the Indian study who received M72/AS01$_E$ reported more AEs within 30 days of vaccination than those in the placebo group (67.4% versus 45.4%). This difference stemmed from more injection-site reactions and flu-like symptoms among M72/AS01$_E$ recipients. Such common, mild, and transient AEs could be taken as evidence of reactogenicity.

In the Swiss study, nasopharyngitis and myalgia were also frequently reported (4 participants each/18.2%) in this group. In the AS01$_E$ alone group, the most frequently reported AEs were nasopharyngitis and headache (both reported in two individuals [25.0%]), and in the placebo group, nasopharyngitis and cough (2 subjects each/28.6%) were the most frequently reported AEs.

Grade 3 unsolicited AEs were infrequently reported (in one or two individuals for a given AE) and only in the M72/AS01$_E$ and AS01$_E$ groups. Vaccine-related unsolicited AEs occurred only in the M72/AS01$_E$ group: two individuals reported feverishness or feeling hot (including one graded 3) and two individuals reported injection site pruritus (none graded 3), all of which resolved within 1–4 days. Two vaccine recipients, both in the M72/AS01$_E$ group, each reported one SAE unrelated to vaccination (appendicitis and cellulitis of the foot).

In both studies, although there were some fluctuations in the levels of hematological or biochemical parameters over time, no clinically relevant changes or vaccine-related trends were observed.

SAEs: In the Indian study, SAEs were reported by 5 HIV-positive M72/AS01$_E$ recipients (of whom 3 were ART-naive) and none of these were M72/AS01$_E$ vaccine-related (Kumarasamy, 2016). There were no SAEs in the Swiss study (Thacher, 2014).

Potential immune-mediated diseases (pIMDs): No pIMDs were reported in the two studies.

HIV parameters: In both studies there were no clinically significant effects of vaccination on the median $CD4^+$ counts or HIV viral loads. In the Indian cohort, compared to the ART-stable cohort, lower median $CD4^+$ counts were reported in the ART-naive cohorts at all time-points, but viral loads were higher in the ART-naive cohort. In the Swiss study, there was a decreased $CD4^+$ T cell count (defined as a decrease of >100 cells/mL from the previous reading), which was reported in five M72/AS01$_E$ recipients (22.7%) and was not considered clinically significant. $CD4^+$ T cell counts in these individuals remained above 200 cells/μL throughout the study. Group median and the majority of individual $CD4^+$ cell counts remained relatively constant during the study.

There were no significant changes in viral load in the Indian study. In the Swiss study, HIV-1 viral loads were undetectable at the time-points measured for all individuals except three M72/AS01$_E$ vaccine recipients, who reported levels exceeding 50 copies/mL at only one post-vaccination time-point each (i.e., 121 copies/mL at Day 30, and 55 and 59 copies/mL at Day 60). These viral load blips were not considered clinically significant (Thacher, 2014).

3. Objectives and Endpoints

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity of M72/AS01$_E$ vaccination	• Solicited adverse events (AEs) through 7 days post each dose of study intervention • Unsolicited AEs through 28 days post each dose of study intervention • All serious adverse events (SAEs) through end of study
Secondary	
• To assess the safety of M72/AS01$_E$ vaccination	• Potential immune-mediated diseases (pIMDs) through end of study • Safety laboratory assessments grade 3 or above through end of study
• To assess the humoral immunogenicity of M72/AS01$_E$ vaccination	• M72-specific antibody titers at Day 1, Day 29, Day 57, Day 210 and Day 390
• To assess the cellular immunogenicity of M72/AS01$_E$ vaccination	• Frequency and magnitude of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by expression of IFN-γ or IL-2 using intracellular cytokine staining (ICS) at Day 1, Day 57 and Day 390
Exploratory	
• To further explore cellular immunogenicity of M72/AS01$_E$ vaccination	• Frequency and magnitude of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by expression of IFN-γ or IL-2 by ICS at Day 29 and Day 210 • Polyfunctionality of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by co-expression of multiple functional markers by ICS
• To assess HIV viral load post-M72/AS01$_E$ vaccination	• Frequencies of participants with confirmed HIV ribonucleic acid ([RNA]>200 copies/mL) at Day 57, Day 210 and Day 390
• To assess changes in CD4$^+$ T cell count from baseline	• Mean changes in CD4$^+$ T cell count from baseline to Day 57, Day 210 and Day 390
• To describe the incidence of suspected TB disease and laboratory-confirmed pulmonary TB disease	• Suspected TB during the study • Laboratory-confirmed pulmonary TB during the study
Other exploratory endpoints may include, but are not limited to, assessing functional antibody profiles in response to vaccination, vaccine-induced changes in innate and myeloid cell populations, and vaccine-induced changes in transcriptomic, proteomic or metabolomic profiles.	

4. Study Design

4.1. Overall Design

Disclosure statement: This is randomized, observer-blind, placebo-controlled, clinical trial of M72/AS01$_E$ tuberculosis vaccine vs. placebo in approximately 400 males and females between 16 to 35 years of age inclusive, who are living with HIV infection, and are virally suppressed (i.e., viral load < 200 copies per mL) on ART.

Interventional model: Participants will be randomly assigned 1:1, to one of two groups in parallel for the duration of the study.

Intervention groups: 2 study groups (M72/AS01$_E$ group and placebo group), will each receive 2 vaccinations administered IM in the deltoid muscle, preferably of the non-dominant arm, one month apart (at Day 1 and Day 29).

- M72/AS01$_E$ group: A 0.5 mL dose of M72/AS01$_E$ contains 10µg M72 reconstituted with AS01$_E$, a GSK proprietary adjuvant system containing 25 µg MPL (3-O-desacyl-4-monophosphoryl lipid A produced by GSK), 25 µg QS-21 (*Quillaja saponaria* Molina, fraction 21). The vaccine will be administered at Day 1 and Day 29.
- Placebo group: Each dose contains 0.5 mL saline (0.9% NaCl). The placebo will be administered at Day 1 and Day 29.

Refer to Section 6.1 for details regarding the vaccine and placebo.

Primary purpose: To assess the safety, as well as immunogenicity of M72/AS01$_E$ vaccine in participants with virally suppressed HIV infection on ART

Safety and immunogenicity outcomes will be followed for 12 months after the second vaccination (end of study) for each randomized participant.

Masking: The study is observer-blind: participants, sponsor, CRO clinical team, laboratory, investigators and site staff will be blinded to the randomization. An Independent Data Monitoring Committee (IDMC) will review unblinded data. The investigational pharmacist preparing study interventions will be unblinded but will not perform other study duties. Refer to Section 6.2.2.

Safety Monitoring: An IDMC will be established to oversee the safety of this study. The IDMC will review unblinded safety data during regular scheduled safety review meetings, and may request additional information, or a pause in recruitment and vaccination, while safety data are being evaluated.

Number of participants: Approximately 400 participants will be enrolled.

Randomization: Participants will be randomized 1:1, stratified by site, and QuantiFERON-TB Gold Plus (QFT) status, based on results at screening.

Adverse events of special interest (AESIs): Protocol-defined pIMDs will be assessed throughout the study.

Analysis: The final analysis will occur after all participants have reached the end of the study (Day 390).

Total duration of study participation: The study duration for each participant, after screening, is approximately 390 days, which includes 2 vaccinations 1 month apart, and 365 days of follow-up post dose 2. Enrollment is expected to take approximately 6 months.

Study sites: Approximately 6 sites in the RSA will participate in this study.

4.2. Scientific Rationale for Study Design

This study design is similar in scope to that of the previous studies that evaluated the M72/AS01$_E$ vaccine in HIV positive populations (refer to Section 2.1), in order to confirm those results in a larger cohort of people living with HIV.

The main inclusion criteria are that the participants with HIV infection (positive HIV antibody) must be on ART for at least 3 consecutive months prior to screening and have HIV RNA <200 copies/mL and CD4 ≥200 cells/µL at screening. They must also have had TB preventive therapy (TPT) in the past.

The rationale is to include healthy people living with HIV who are receiving ART. These selection criteria are aimed to enroll individuals at low risk for opportunistic infections (OI), immune reconstitution inflammatory syndrome (IRIS) and new ART-related side effects during the study. Stable ART for at least 3 months would reduce the risk of new onset AEs possibly related to the regimen. Most AEs from ART occur during the first days and weeks of its initiation, and any AEs resulting in regimen modifications would likely have occurred prior to 3 months. IRIS generally occurs during the first 3 months of ART initiation as an inflammatory response to undiagnosed or subclinical OI. It is more common in people with low $CD4^+$ count (who are excluded from this study), and can be severe and life-threatening. $CD4^+$ count < 200 cells/µL is considered severe immune deficiency, necessitating medications for OI prophylaxis. By enrolling people with $CD4^+$ above this threshold, there is less risk for IRIS and it avoids the need for concomitant OI prophylaxis. Viral load < 200 copies/mL indicates successful ART. ART is the standard of care worldwide regardless of HIV symptoms, $CD4^+$ counts or viral load levels. TPT reduces risk for TB disease and is standard of care for all people living with HIV. Therefore, in this study, only participants who have had TPT prior to screening will be included.

4.3. Justification for Adjuvant System and Dose

A previous study, TB-009, was conducted to evaluate the different adjuvant systems, AS01 versus AS02, and to determine the antigen/adjuvant dose for further development. This study enrolled PPD positive adults with no history of TB, living in The Philippines, a TB endemic region. Adjuvanted vaccine formulations used were:

- M72 (40 µg)AS01$_B$,
- M72 (20 µg)AS01$_E$,
- M72 (10µg)AS01$_E$
- M72 (10 µg)AS02$_D$.

This study confirmed that M72/AS01 vaccine formulations induced a higher cell-mediated immune response compared to M72/AS02 vaccine formulations and showed that the lower M72 dose (10 µg) induced immune responses that were comparable to those induced by higher M72

doses (20 and 40 µg). Furthermore, all adjuvanted vaccine formulations had a similar safety and reactogenicity profile.

The low dose antigen-Adjuvant System combination M72(10µg)AS01$_E$ was thus selected as the TB vaccine candidate for further evaluation in clinical trials including the phase 2b TB-018 efficacy study (Van Der Meeren, 2018).

The schedules other than 0 and 1 month have not been explored, and this schedule was shown to be efficacious in Phase 2b. To minimize risk, the scientific community agreed that the 0, 1 schedule should be maintained through Phase 3 and licensure (WHO, 2019e).

The selection of the dose and schedule of vaccination in this protocol is also the same as in the previous phase 2 studies in people living with HIV (TB-011 and TB-014).

Vaccination schedules in all previous M72/AS01$_E$ studies consisted of 2 doses given one month apart, except for the TB-013 study in which 100 participants (1/3) received only one dose. All doses were administered IM in the deltoid region of the arm or in the anterolateral thigh of infants (TB-013).

4.4. End of Study Definition

A participant is considered to have completed the study if he or she completes the final visit, Visit 7 (Day 390).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Recruitment

Participants will be recruited from communities with known high burden of TB transmission and disease. Good participatory practices will be followed and site staff will work closely with community organizations and community leaders.

Various methods of recruitment may be used, such as community information sessions, advertising, referrals, word-of mouth, or solicitation through participants previously known to the clinical site.

All recruitment materials will be approved by the appropriate Institutional Review Board/s (IRBs) or Independent Ethics Committee/s (IECs). Interested participants will be invited to participate in the informed consent and assent process, depending on age (see Section 9.5.2).

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria are met:

Age

1. Participant must be 16 to 35 years of age inclusive, at the time of signing the informed consent or assent.

Type of Participant and Disease Characteristics

2. Participant with documented HIV infection who fulfill all of the following:
    - Has reactive anti-HIV antibody at screening
    - On ART for at least 3 consecutive months at screening
    - Has documented HIV RNA <200 copies/mL at screening
    - Participants with $CD4^+$ cell counts ≥200 cells/μL at screening
3. Participants have had TPT in the past and are not receiving TPT at the time of screening, according to the judgment of the investigators
4. Participants who are healthy as determined by medical evaluation including medical history, physical examination and laboratory tests

Informed Consent

5. Capable of giving signed informed consent and informed assent (if appropriate), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) or informed assent form, and in this protocol (see Section 9.5.2 for details regarding the informed consent process).

Sex

6. Female participants of childbearing potential must agree not to become pregnant from the time of study enrollment for one year after study intervention. Women physically capable of pregnancy, sexually active and has no history of hysterectomy or tubal ligation or menopause must agree to use an effective method of avoiding pregnancy during this period. Refer to Section 9.7 for details.

Additional requirements:

7. Participants who agree to stay in contact with the study site for the duration of the study, provide updated contact information as necessary, and have no current plans to relocate from the study area for the duration of the study.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria are met:

Medical Conditions

1. Acute illness or fever ≥99.5°F (or ≥37.5°C) on Day 1
2. History of active TB disease
3. Evidence of active TB disease with any of the following:
    - Have symptoms or signs of TB disease
    - Have a positive sputum Xpert MTB/RIF assay (only in participants with sputum sample at screening)
    - Are on treatment for active TB disease
4. Evidence and/or history of clinically significant medical conditions (other than HIV infection) as judged by the investigator, including malignancies
5. Any current medical, psychiatric, occupational, or substance abuse problems that, in the opinion of the investigator, will make it unlikely that the participant will comply with the protocol

Prior/Concomitant Therapy

6. Any medications or other therapies that may impact the immune system such as immune globulin, interferon, immunomodulators, cytotoxic drugs or other drugs known to be frequently associated with major organ toxicity as determined by the investigator, within 90 days prior to Day 1
7. Immunosuppressive agents including systemic steroids - prior corticosteroid therapy within 90 days prior to Day 1 (permitted: 5mg/day prednisone equivalent, inhaled, topical, and intra-articular corticosteroids)
8. Receipt or donation of blood or blood products within 90 days prior to Day 1 or planned receipt or donation during the study period.
9. Receipt of any vaccine in the period starting 7 days before, and ending 7 days after, each dose of the study vaccine. Refer to Section 6.4.

Prior/Concurrent Clinical Study Experience

10. Participation in an interventional clinical trial and/or receipt of any investigational drug within 180 days prior to signing informed consent or assent
11. History of previous administration of experimental Mtb vaccine

Diagnostic Assessments

12. Safety laboratory values outside of normal range, for age and sex that are suggestive of a disease state (Grade 1 abnormalities, as per DAIDS toxicity table version 2.1, will not lead to exclusion if the investigator considers them not clinically significant.)

13. Urinalysis abnormality greater than Grade 1 on the Toxicity Scale (with the exception of hematuria in a menstruating female), or urinalysis abnormality judged clinically significant by the investigator
14. Current hepatitis B and/or hepatitis C infection
15. Indeterminate QFT result

Other Exclusions

16. History of allergy or hypersensitivity to the study drug, excipients or related substances
17. Shared residence with an individual who is receiving TB treatment or with someone who is known to have incompletely treated TB, e.g., Xpert MTB/RIF assay-positive, PCR-positive, culture-positive, smear-positive TB, or clinically diagnosed unconfirmed TB
18. Female participants with any one of the following conditions: currently pregnant or lactating/nursing; having positive serum pregnancy test during the screening window, planning a pregnancy within 1 year after first dose of study intervention
19. Individuals who are acting as study personnel or immediate family members (brother, sister, child, parent) or the spouse/partner of study personnel.
20. Child in Care*

*Defined as a child who is under the care (control or protection) of an agency, organization, institution or entity by the courts, the government body, acting in accordance with powers conferred in them by law or regulations. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangements fall within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, consent status and any SAE.

Rescreening is only permitted under the following conditions:

- If a participant presents with an acute illness day of first study intervention, e.g., elevated temperature, and meets all other inclusion/exclusion criteria and is rescreened within the originally defined screening window (Section 1.2).
- When there are technical difficulties with phlebotomy at screening (e.g., laboratory reports hemolyzed blood), technical error in running the laboratory tests, or an abnormal urine analysis (e.g., due to menstruation or urinary tract infection).

Rescreened participants should be assigned the same participant number as for the initial screening.

Refer to Section 9.5.2 regarding consent process for rescreened participants.

6. Study Intervention

Study intervention is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Participants randomized to the vaccine group will receive 2 doses of the M72/AS01$_E$ candidate vaccine which contains 10 µg of a recombinant fusion protein derived from the *Mtb* antigens *Mtb*32A and *Mtb*39A (M72), and the adjuvant, AS01$_E$.

A 0.5 mL dose of M72/AS01$_E$ contains 10µg M72 reconstituted with AS01$_E$, a GSK proprietary adjuvant system containing 25 µg MPL (3-O-desacyl-4-monophosphoryl lipid A produced by GSK), 25 µg QS-21 (*Quillaja saponaria* Molina, fraction 21; licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation), and liposomes.

The control group will receive a 0.5mL saline (0.9% NaCl) placebo per dose.

Table 4: Study Interventions

	M72/AS01$_E$ Vaccine	**Control**
Intervention Name	M72/AS01$_E$ *Mycobacterium tuberculosis* vaccine	Normal saline
Unit Dose Strength	10 µg	Normal saline (0.9% NaCl)
Dosage Volume	0.5 mL per injection	0.5 mL per injection
Route of Administration	IM injection	IM injection

6.1.1. Administration

Both the vaccine and placebo injections will be administered IM in the deltoid muscle of the upper arm, preferably the non-dominant arm, using standard technique. A standard syringe and needle will be available locally at site.

The M72/AS01$_E$ vaccine is slightly opaque compared to the transparent saline placebo. The unblinded investigational pharmacist will provide M72/AS01$_E$ and placebo to the clinic as unit-dose syringes, which will be identified with the participant identification number, date and time of dose preparation, and the volume prepared. An investigator (i.e., physician) must be present in the clinic at the time of administration. Labels will be prepared and provided by the CRO.

Before administering the injection, the study intervention administrator must check that the syringe is identified with the correct participant identification number and check the date and time the dose was prepared.

6.1.2. Preparation/Handling/Storage/Accountability

The M72/AS01$_E$ vaccine will be supplied as a lyophilized cake for reconstitution with the AS01$_E$ adjuvant system.

The normal saline placebo for injection will be prepared as described in 6.1.1.

The vaccine must be stored between +2°C to +8°C in a secured location with no access for unauthorized personnel. Reconstituted vaccine must be stored between +2°C to +8°C and administered as soon as possible and within 8 hours after reconstitution. Any reconstituted vaccine not used within 8 hours must be discarded. Exposure to light should be kept to a minimum.

The saline placebo must also be stored in a secured location between +2°C to +8°C with no access for unauthorized personnel.

The study pharmacist (or designee) must confirm appropriate temperature conditions have been maintained during transit and during site storage for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. Upon receipt of study vaccine supplies, the authorized site staff must immediately inspect all kits for damage. Any damage or discrepancies from the packing list must be documented and promptly discussed with the sponsor and the study monitor to determine the appropriate action.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The principal investigator (PI) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Authorization for any unused study vaccine and supplies to be destroyed is the responsibility of the sponsor. Unused supplies will be destroyed according to the facility's SOPs or per local regulations. Any disposal of study vaccine conducted at the clinical site must be documented in the study file.

Further guidance and information for the preparation, handling, storage and accountability are provided in the Study Pharmacy Manual.

6.1.3. Vaccine Administration Error

Vaccine administration error is defined as the administration of a dose of the study vaccine that was not intended as instructed or by a route that is different from the intended route of administration. Each vaccine dose will be prepared by reconstituting fully the contents of one vial containing the antigen with the contents of one vial of the adjuvant, and then drawing out the reconstituted vaccine content (0.5 mL) into the dosing syringe. In case of any deviation, the instructions in the pharmacy manual and the IB are to be followed.

6.2. Measures to Minimize Bias: Randomization and Blinding

6.2.1. Randomization

Participants will be randomized to one of two interventions (M72/AS01$_E$ or placebo) based on a randomly-generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Voice/Web Response System (IVRS/IWRS).

Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and instructions for the IWRS will be provided to the study sites.

The randomization schedule will be prepared by a statistician who will not be involved in the analysis of the study in order to maintain the blind of the study team.

The day of randomization for each participant will be Study Day 1. Randomization will be stratified by site and QFT status.

6.2.2. Masking

The study will be conducted as an observer blind study because of the difference appearances of the vaccine and placebo.

The study team will remain blinded until the end of the study, and the laboratory staff will remain blinded until all laboratory studies have been completed.

Only the following people will have access to treatment allocation while the study is blinded:

- Investigational pharmacists preparing the study interventions
- Biostatistician preparing the randomization list
- Biostatistician preparing the IDMC data
- IDMC members
- Unblinded study monitors.

All unblinded persons must take care to not reveal individual group assignments to any other member of the study team. The investigational pharmacist preparing study interventions, will be unblinded but will not perform other study duties.

Unblinded study personnel must not participate in the evaluation of AEs. A delegation of authority log will be maintained by the site and will identify the individual(s) with access to study blinding information.

6.2.3. Blind Break

The IVRS/IWRS will be programmed with blind-breaking instructions. In addition, instructions on emergency unblinding in case of system outage will be provided. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

6.3. Study Intervention Compliance

Participant compliance with study intervention will be recorded on his/her CRF.

6.4. Concomitant Therapy

As part of the inclusion criteria, participants must have documentation in the CRF that they have been on ART for at least 3 consecutive months prior to screening and should remain on ART throughout the study period. Modifications of ART for clinical reasons are allowed. Discontinuation of ART is not cause for study withdrawal.

Receipt of any vaccine 7 days before and 7 days after either Dose 1 or Dose 2 is prohibited during the study, and will lead to study withdrawal. Refer to Section 7.2.

All vaccines received within 30 days prior to the first study vaccine administration and throughout the study will be recorded for each participant.

Any prescription medication, anti-inflammatory drugs and antipyretic drugs*, or vaccine that the participant receives from enrollment through study must be recorded at specified timepoints as shown in the SoA, along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

* The use of anti-inflammatory and antipyretic medication should be discouraged during the first 28 study days (days 1 through 28 after each dose administered).

Information regarding all immunosuppressant therapy/medications and TB curative treatment, experimental drugs or vaccines, and receipt or donation of blood products will be collected and monitored through the last study visit.

Note that any of these concomitant therapies or medications are not allowed in the study and their administration will lead to withdrawal from the study.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5. Dose Modification

There are no dose modification specifications.

All participants will receive 2 doses by injection of either M72/AS01$_E$ vaccine or placebo as described in Section 6.1.1.

6.6. Intervention after the End of the Study

There is no intervention planned after the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of / Withdrawal from Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention.

See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

A 'withdrawal' from the study treatment refers to any participant who does not receive the complete treatment, i.e., when no further planned dose (i.e., dose 2) is administered from the date of withdrawal. A participant withdrawn from the study intervention may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

All data collected until the date of withdrawal/last contact of the participant will be used for the analysis.

Information relative to premature discontinuation of the investigational vaccine will be documented in the CRF. The investigator will document whether the decision to discontinue further vaccination was made by the participant or by the investigator (or designee), as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

7.1.1. Contraindications to the Second Dose

The following events constitute absolute contraindications to further administration of M72/AS01$_E$ or placebo. If any of these events occur during the study, the participant must not receive the second dose but may continue other study procedures at the discretion of the investigator.

- Hypersensitivity reaction, including anaphylaxis, following the administration of the first dose
- Pregnancy
- Auto-immune disease
- Discovery of any health condition which, in the investigator's opinion, places the participant at increased risk from receipt of further investigational product; or discovery of a change in the participant's status which renders him/her unable to comply with protocol-mandated safety follow-up.

The vaccine doses can be administered to participants with a minor illness (i.e., mild diarrhea, mild upper respiratory infection, etc.) without fever (fever ≥37.5°C/99.5°F oral body temperature, or equivalent). If the participant has fever, with or without a minor illness at the time scheduled for vaccination, the participant may be vaccinated at a later date, within the specified time window for that visit or withdrawn at the discretion of the investigator.

7.2. Participant Withdrawal from the Study

From an analysis perspective, a 'withdrawal' from the study refers to any participant who did not come back for the concluding visit (Visit 7 [Day 390]).

All data collected until the date of withdrawal/last contact of the participant will be used for the analysis.

A participant is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this participant from the date of withdrawal/last contact.

Information relative to the withdrawal will be documented in the CRF including date and reason. A withdrawal from the study because of an SAE/AE must be clearly documented in the CRF. Investigators will follow participants who are withdrawn from the study as result of a SAE/AE until resolution or stabilization of the event.

The investigator will document whether the decision to withdraw a participant from the study was made by the sponsor or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (specify)
- Consent withdrawal, not due to an adverse event*
- Moved from the study area
- Lost to follow-up
- Other (specify).

*If a participant withdraws consent, the reason, if specified, will be documented in the CRF.

A participant may, at the investigator's discretion, be withdrawn from the study if any one of the below conditions apply. Participants with the below conditions will be followed for safety as described in the protocol, without any of the protocol-required blood draws.

- Development of active TB or receipt of curative anti-tuberculous therapy
- Development of autoimmune disease or immunosuppression, or an AESIs
- Receipt of investigational drug therapy or investigational vaccine outside of the study or concomitant treatment or therapies noted as exclusion criteria
- Pregnancy
- Receipt of any vaccine 7 days before and 7 days after either Dose 1 or Dose 2.

A participant may withdraw (or a participant's parent or guardian (a guardian is a legally acceptable representative [LAR]) may withdraw the participant) from the study at any time or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

If the participant withdraws consent the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits (3 failed visits) and is unable to be contacted by the study site (3 failed attempts per failed visit).

If a participant fails to return to the clinic for a required study visit, the following actions must be taken.

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a home visit by a member of the study team). These contact attempts should be documented in the participant's medical record and the CRF.

Should the participant continue to be unreachable, he/she will be considered lost to follow-up from the study.

7.4. Pausing Guidelines

Pausing guidelines are put in place to address events necessitating a pause in enrollment and in participant dosing, and an IDMC review. Therefore, these guidelines are in effect during the active enrollment and dosing period.

Refer to Section 9.5.1 regarding the IDMC, established to oversee the safety of this study

Any of the below conditions, if identified either by an investigator, the sponsor or the IDMC, will trigger a pause of the enrollment and pause of administration of study intervention until the IDMC has reviewed the safety data and made a recommendation on how to proceed:

1. One report of anaphylaxis with or without bronchospasm within 4 hours of injection, indicative of an immediate hypersensitivity reaction to the study injection
2. 1% of the safety population and at least two participants experience an SAE judged as related to study intervention by the investigator

3. 20% of participants and at least 20 participants experience a Grade 3 or higher event related to study vaccine, as judged by the investigator, with the exception of expected local reactions or local injection site reactions that decrease to < Grade 3 within 48 hours.

If an investigator observes that pausing guideline 1 or 2 is met, the investigator will inform the sponsor or delegate as soon as possible and within 24 hours of the observation. The sponsor or delegate will notify all study investigators and the IDMC members of the pause in enrollment as soon as possible and within 24 hours of receiving notification of the condition being met. The IDMC members will review all relevant safety data, convene an urgent ad hoc review meeting and make a recommendation to the sponsor with regards to maintaining the pause in enrollment or resuming enrollment.

If, during one of its scheduled or ad-hoc meetings, the IDMC observes that a pausing guideline is met, the IDMC Chair or delegate will inform the sponsor as soon as possible and within 24 hours of the identification of the condition being met. If the IDMC has sufficient information to recommend that enrollment resume, this can be communicated to the sponsor within the same timeline. The sponsor or delegate will notify all study investigators of the pause in enrollment as soon as possible and within 24 hours of receiving notification from the IDMC.

If the sponsor or delegate observes that a pausing guideline is met, the sponsor will notify all study investigators and the IDMC members of the pause in enrollment as soon as possible and within 24 hours. The IDMC members will review all relevant safety data, convene an urgent ad hoc review meeting and make a recommendation to the sponsor with regards to lifting or maintaining the pause in enrollment.

The IDMC may recommend resumption of enrollment with or without changes to the protocol. The final decision to pause or resume study activities will always be the responsibility of the sponsor. All IDMC recommendations will be stored according to the IDMC Charter.

All sponsor decisions will be documented in a memorandum to the study file. The sponsor or delegate is responsible for prompt communication to all relevant study sites of decisions related to pausing or resuming the study activities, including notification to the PI, relevant IRBs/IECs and regulatory authorities.

The clinical sites will be allowed to resume activities only upon receipt of written notification from the sponsor.

7.5. COVID-19 Contingency Plans

In the event that coronavirus disease, COVID-19, affects the conduct of this trial, the sponsor will evaluate if in-person visits are necessary to fully assure the safety of trial participants and whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment such as local labs or home visits) could be implemented when necessary and feasible, and would be sufficient to assure data integrity and safety of participants (FDA, 2020; SACRA, 2020; SAPHRA, 2020).

Any contingency plans must be sufficient to assure the safety of trial participants. Changes in study visit schedules, missed visits, or withdrawal of the study intervention or participant

discontinuations may lead to missing information (e.g., for protocol-specified procedures) must be captured in the case report form that explains the basis of the missing data (i.e., COVID-19).

Approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites must be documented. Depending upon the nature of the changes described above, a protocol amendment may be required under the applicable regulations.

Deviations because of COVID-19 will be described in the clinical study report or in a separate study-specific document) including but not limited to the following:

- Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.
- A listing of all participants affected by the COVID-19 related study disruption by unique participant number identifier and by investigational site, and a description of how the individual's participation was altered.
- Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.2).

Prior to any study procedure, all eligible participants will be assigned a unique participant identifier. This participant identifier will be used throughout the study for participant identification.

Screening for eligibility assessment will occur after informed consent, and as applicable, assent, is obtained (see Section 9.5.2 for the consent/assent process). Eligibility for randomization will be based on the inclusion and exclusion criteria (described in Sections 5.1 and 5.2, respectively).

Eligibility criteria will be checked during the screening process and prior to study intervention administration to ensure that all participants enrolled meet all of the inclusion criteria and none of the exclusion criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

To evaluate eligibility criteria, a medical history and physical examination including vital signs, height, and weight will be performed. In addition, safety laboratory tests (hematology and chemistry), and urinalysis (including microscopy) as well as a QFT TB test, sputum Xpert MTB/RIF assay, $CD4^+$ cell count, HIV viral load, HIV serology, hepatitis B and C screening, and a serum pregnancy test (females only) will be performed. Refer to Section 8.2 for details regarding these procedures.

The investigator must document confirmation of eligibility prior to randomization.

All protocol-required safety laboratory tests (hematology, chemistry, and urinalysis) as well as a QFT TB test, sputum Xpert MTB/RIF assay, CD4+ cell count, HIV viral load, HIV serology, hepatitis B and C screening, and a serum pregnancy test (females only) will be performed by the central laboratory, Bio Analytical Research Corporation RSA (BARC SA or similar).

Urine pregnancy tests will be performed by the study site.

Assays for secondary, and exploratory endpoints will be carried out in laboratories outside of the RSA.

8.1. Efficacy Assessments/Immunogenicity

Efficacy of the M72/AS01$_E$ vaccine will not be measured in this study. Instead, the study is designed to evaluate safety and immunogenicity of the vaccine.

8.1.1. Humoral Immunogenicity

Blood samples for immunogenicity evaluation of M72-specific IgG antibody in serum will be collected per SoA (Table 2). On Day 1 and Day 29 visits, samples will be collected prior to study intervention administration. Humoral M72-specific IgG antibodies will be measured by enzyme-linked immunosorbent assay (ELISA).

8.1.2. Cell-Mediated Immune Responses

Blood samples for CMI responses will be collected as shown in the SoA (Table 2).
On Day 1 and Day 29 visits, samples will be collected prior to study intervention administration.

Peripheral blood mononuclear cells (PBMCs) will be isolated and analyzed using intracellular cytokine staining (ICS) to assess the frequency, magnitude and polyfunctionality of M72-specific $CD4^+$ and $CD8^+$ T-cell responses. M72-specific $CD4^+$ and $CD8^+$ T cells expressing multiple cytokines will be measured upon short-term in vitro stimulation of PBMCs.

For the secondary objective, frequency and magnitude of M72-specific CD4+ and CD8+ T-cell responses will be measured by expression of IFN-γ or IL-2 at Days 1, 57 and 390 to characterize the vaccine-induced immune response at baseline, peak immunogenicity and long-term memory, respectively.

If responses at peak or memory are lower than expected compared to historical data from previous M72 vaccine studies, additional timepoints may be assessed to further characterize the kinetics of the cellular vaccine-induced immune response in HIV-positive study participants.

For exploratory objectives, polyfunctionality of M72-specific CD4+ and CD8+ T-cell responses will be measured to support the exploratory objective by analysis of the co-expression of multiple functional markers by ICS.

8.1.3. Subset Assessments

It may not be necessary to test all participants for immunogenicity. Strategies to sample only a portion of participants for immunogenicity may be considered and final plans will be documented in a separate statistical analysis plan prior to data unblinding.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

Safety outcomes will include:

- Solicited AEs: local injection site pain, redness, and swelling, and general AEs including headache, fatigue, malaise, myalgia, gastrointestinal symptoms, and fever (defined as a temperature ≥37.5°C [99.5°F]).
- Unsolicited AEs
- All SAEs
- Vaccination-related SAEs
- pIMDs
- Safety laboratory assessments ≥grade 3.

Refer to Section 8.3 for details regarding AEs and SAEs, and Section 8.2.5 for safety laboratory assessments.

8.2.1. Physical Examination and Medical History

A medical history and physical examination will be conducted at screening to assess enrollment eligibility. Only participants who are considered healthy by the investigator will be enrolled.

All conditions that exist prior to administration of study intervention will be recorded in the medical history. Day to day fluctuations in these conditions that do not represent a clinically significant change in the participant's status will not necessarily be reported as AEs.

Physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems, as well as assessment of height and weight, body temperature, and resting vital signs (blood pressure, pulse and respiratory rate). Vital signs will be measured after at least 5 minutes of rest in a quiet setting without distractions. Vital signs will be taken prior to each dose administration.

As part of the history/physical examination at each visit, a TB symptom/sign checklist from RSA TB guidelines will be used. This will include TB contact history. The TB symptom/sign checklist in the eCRF includes:

- Cough for longer than 2 weeks
- Fever for longer than 2 weeks
- Fatigue for longer than 2 weeks
- Night sweats for longer than 2 weeks
- Loss of weight or insufficient weight gain or growth
- Other.

If TB is suspected, potential participants would be managed according to standard of care.

8.2.1.1. Interim History and Focused Physical Examination

An interim history will be taken on Day 1 and all subsequent visits, as indicated in the SoA. A focused physical examination will be performed if indicated by interval history and may include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Body weight will be measured at each visit. A TB symptom screen and TB contact history update will also be included at each visit.

8.2.2. Pregnancy Status Assessment

A serum βHCG test will be performed at screening, Day 1 (Visit 1), Day 29 (Visit 3), Day 57 (Visit 5) and Day 210 (Visit 6) and Day 390 (Visit 7).

A urine βHCG test will be performed at Day 1 (Visit 1, prior to enrollment and dose 1) and Day 29 (Visit 3, prior to dose 2).

During the study, participants will be asked about pregnancy at each time point indicated in the SoA (Section 1.2). If a pregnancy is reported, the investigator should inform the Medical Monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 9.7.

If a participant becomes pregnant during the study, she will be withdrawn from all study procedures going forward, i.e., dose administration, blood-draws and laboratory evaluations described in the SoA will not be performed once a participant is known to be pregnant.

However, she will be encouraged to continue in the study for safety follow-up.

Details of all pregnancies will be collected after the start of study intervention and until the end of the study.

8.2.3. Pre- and Post-Study Intervention Safety Monitoring

On Day 1 (Visit 1) and Day 29 (Visit 3), prior to vaccine/placebo administration, vital signs will be taken.

Participants will remain under observation for at least 30 minutes after receiving the injection.

Allergic reactions to vaccination are possible, therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a physician trained to recognize and treat anaphylaxis must be present in the clinic during vaccination and the post-vaccination monitoring period.

8.2.4. Diary Card and Daily Temperature Monitoring

On Day 1 (Visit 1) and Day 29 (Visit 3), participants will be given a diary card and receive guidance (training) on how to fill in the card. Participants will also receive a digital thermometer.

The diary card will be used by the study participants to record the duration and intensity (Grade 1, 2, 3, or 4) of solicited local and general AEs, and any unsolicited AEs, for 7 days following vaccination. The diary card will also allow for unsolicited AEs to be recorded.

The diary card will be collected and reviewed by the PI (or designee) 7 days after each dose, i.e., on Day 8 (Visit 2) and Day 36 (Visit 4). No changes to the diary card will be permitted, however, any verbally recalled information provided by the participant or parent or guardian/LAR during review of the diary card will be documented in the source document and reported as an AE.

A memory aid will be distributed to the participant on Day 8 (Visit 2) and Day 36 (Visit 4) and the participant will receive guidance (training) to record any general AEs or unsolicited AEs, using the aid (any local injection site AE reported after Day 8 will be considered an unsolicited AE).

The memory aid will be collected one month after each dose, i.e., on Day 29 (Visit 3) and Day 57 (Visit 5).

Memory aids and diary cards are regarded as source documents for the study.

8.2.5. Clinical Safety Laboratory Assessments

Safety laboratory assessments will be performed at screening and prior to each dose administration.

Laboratory values from blood/urine sample collected at screening outside the normal range that are suggestive of a disease state (i.e., values greater than Grade 1) will lead to exclusion from study enrollment, with the exception of any grade hematuria in a menstruating female, or a urinalysis abnormality judged not clinically significant by the investigator.

Refer to Section 9.8, for toxicity table for grading laboratory indices.

Clinical safety laboratory parameters that will be evaluated at screening include:

- Hematology: hemoglobin (Hgb), white blood cells (WBC), platelets
- Serum chemistry: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and total bilirubin
- Urinalysis by dipstick: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase.
- Urine microscopy.

Abnormal results and findings that make the participant ineligible will be discussed with the participant and the participant will be referred for follow-up care with their healthcare provider if necessary.

Information about the laboratory(ies), including any instructions for performing and interpreting specific tests, will be maintained in the investigator's study files.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

An abnormal laboratory value should be deemed clinically significant if either of the following conditions are met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA.

Hematology and serum chemistry will be monitored on Day 1 and Day 29.

If laboratory values from non-protocol specified laboratory assessments require a change in participant management or are considered clinically significant by the investigator (e.g., AE or SAE), then the results must be recorded in the CRF.

All protocol-required safety laboratory tests will be performed by the central laboratory, Bio Analytical Research Corporation RSA (BARC SA or similar).

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

8.2.6. HIV Antibody Assessment and HIV Viral Load Assessment

To be eligible for the study, participants must have reactive anti-HIV antibody at screening and be on ART for at least 3 consecutive months at the time of screening and have HIV viral load <200 copies/mL.

ART initiation date will be documented at screening.

To assess that all participants have HIV viral load <200 copies/ mL on ART, an HIV viral load assessment (copies/mL) will be performed as shown in the SoA (Section 1.2).

If an enrolled participant has HIV viral load> 200 copies/mL, confirmed HIV RNA rise as determined by the HIV viral load assessment per SoA (Section 1.2) should be managed according to standard of care.

At screening, $CD4^+$ T cell counts will be measured to ensure that all enrolled participants have ≥200 cells/µL.

Once enrolled, participants may remain in the study regardless of their ART status or HIV viral load and $CD4^+$ T cell counts.

8.2.7. QFT assessment for TB

QuantiFERON-TB Gold Plus (QFT) testing (Cellestis Ltd., Australia) will be conducted at screening, and the last visit (Section 1.2).

Participants may be enrolled in this study regardless of QFT status (positive or negative). An indeterminate QFT test at the screening visit would render the participant ineligible for the study.

8.2.8. Sputum Xpert MTB/RIF

A single self-expectorated sputum will be collected for Xpert MTB/RIF assay from all participants at screening and from participants with suspected TB, at study visits. Participants with a positive sputum Xpert MTB/RIF assay at screening (if sputum is able to be collected) are ineligible for the study. All participants with a positive sputum Xpert MTB/RIF assay and/or suspected TB should be referred for further management per standard of care. No sputum induction will be done. Sputum Xpert MTB/RIF assay is not required in participants who are unable to produce sputum.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs, SAEs, SUSARs, and AESIs can be found in Appendix 1, Section 9.6.1, and 9.6.2, 9.6.3, 9.6.4, respectively.

AEs will be reported by the participant (or, as appropriate, the participant's legally authorized representative). Biochemistry and/or hematology findings may also qualify as AEs if the investigator considers them as such.

Study nurses and physicians are responsible for collecting and documenting information and events that would potentially meet the definition of an AE. However only the investigator (study physician) is responsible for assessment, including assignment of causality and intensity, reporting and management of all AEs. The investigator is responsible for following up all AEs regardless of their relatedness to the study intervention or study procedures, or that caused the participant to discontinue the study (Sections 7, 8.3.1, and 8.3.3).

Refer to Table 5 for the required time periods for collection of each type of AE.

8.3.1. Time Period and Frequency for Collecting AE, SAE, and Pregnancy Information

Table 5: Collection Period for all AEs and Pregnancies

Type of Event	Collection Time Period
Any AE, SAE, or AESI	From time of ICF and/or IAF is signed until dosing at Day 1
All solicited AEs	7 days after each dose
Unsolicited AEs	28 days after each dose
All SAEs, AESIs and Pregnancies	Day 1 through Month 13 (Day 390) (end of study)

Distribution and collection days for diary cards are shown in the SoA (Section 1.2).

All SAEs and AESIs will be reported to the sponsor or designee within 24 hours, as indicated in Appendix 1, Section 9.6.6. The investigator will submit any updated SAE data to the sponsor or designees within 24 hours of being available

Investigators are not obligated to actively seek AEs or SAEs after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be related to the study intervention or study participation, the investigator must notify the sponsor or designee within the same 24 hours timeline.

8.3.2. Method of Detecting AEs and SAEs

The methods of recording and follow-up of AEs and SAEs are provided in detail in Appendix 1, Section 9.6.5, which includes assessments of intensity, causality, expectedness and outcome of AEs and SAE.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading questions are the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). Refer to Section 9.6.5 for details regarding recording and follow-up.

8.3.3.1. AE Intensity

Unsolicited AEs will be classified by the investigator as mild (Grade 1, not interfering with normal daily activities), moderate (Grade 2, interfering with normal daily activities), severe (Grade 3, preventing normal daily activities) or potentially life-threatening (Grade 4). Refer to Appendix 1, Section 9.6.5.1 for details. Solicited AEs will be graded by the participant using the diary card.

8.3.3.2. AE Causality

All AEs will be evaluated by the PI or medically qualified designee (i.e., investigator, study physician) to assess the relationship between study intervention and AE. Careful medical judgement should be exercised to determine the level of causal relationship between an AE and the study intervention. The causality will be assessed as related or not related.

The sponsor or designee will have the opportunity to confirm the seriousness and case causality based on the clinical judgement of the Medical Monitor and sponsor designee. If a serious adverse event is considered unrelated by the investigator but the sponsor believes that there is a reasonable possibility that the event is related, the sponsor will upgrade the case to a ‘related’ status. The sponsor or designee will never downgrade a case from serious to non-serious.

Refer to Section 9.6.5.2 for details.

8.3.3.3. AE Resolution

All AEs/SAEs must be followed until resolution. Refer to Section 9.6.5.4 for details.

8.3.4. Regulatory Reporting Requirements for SAEs

Refer to Section 9.6.6 for details regarding SAE reporting.

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor or delegate has a legal responsibility to notify both the local regulatory authority and potentially other regulatory agencies about the safety of the study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators. The sponsor is responsible for the determination of expectedness according to the applicable version of the Reference Safety Information of the Investigator's Brochure.

All fatal and life-threatening serious unexpected suspected adverse drug reactions (SUSARs) are to be reported to SAHPRA within 7 calendar days after first knowledge by the sponsor or its delegate, with a complete report to be submitted within an additional 8 calendar days.

Other SUSARs that are not fatal or life threatening need to be reported no later than 15 calendar days after first knowledge by the sponsor or delegate.

SUSARs and other applicable safety information submitted to the applicable regulatory authorities will be distributed to the investigators for awareness. An investigator who receives a SUSAR report or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and file it. A tracker of all such reports received from the sponsor will be maintained by the site. The investigator will notify the IRB/IEC, if appropriate and according to local requirements. IRB/IEC submissions will be conducted per the local IRB/IEC standard operating procedures (SOPs).

The sponsor will prepare, distribute and submit SUSARs and other applicable reports according to local regulatory requirements. The CRO, on behalf of the sponsor will submit the corresponding reports to the regulatory authorities.

Refer to Section 9.6.6 for details regarding SAE reporting.

8.3.5. Death Events

Any untoward medical occurrence resulting in death is reported as an SAE. The cause of death will be appropriately documented in the SAE report form and supporting evidence will be provided.

8.3.6. *Mtb* Infection and Disease

Active surveillance for signs and symptoms compatible with incident TB disease, e.g., cough, fever, fatigue or night sweats, for longer than 2 weeks, or loss of weight, will continue throughout the study.

Any cases of TB disease will be summarized.

8.3.7. HIV RNA and CD4+ T Cell Count Analysis

The proportion of participants with confirmed HIV RNA > 200 copies/mL will be summarized.

Changes in $CD4^+$ T cell counts will be summarized by treatment group and time point, with 95% confidence intervals (CIs).

8.4. Treatment of Overdose

Not applicable

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this vaccine study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Exploratory Biomarkers

Collection and analyses of blood samples for biomarker research is an exploratory objective. Analytic approaches for the exploratory endpoints below will be informed by best practice and the most recent advances in biomarker discovery and systems biology, including the identification of vaccine-induced correlates of protection (CoP) in the currently planned retrospective analysis of TB-018 samples. Putative CoP will be tested in this trial to confirm that HIV infection does not interfere with the induction of CoP by vaccination.

Exploratory endpoints may include, but are not limited to, assessing functional antibody profiles in response to vaccination, vaccine-induced changes in innate and myeloid cell populations, and vaccine-induced changes in transcriptomic, proteomic or metabolomic profiles.

PBMC, plasma, serum and whole blood samples will be collected at time points likely to show peak responses for cellular, humoral, and transcriptomic responses, respectively. Refer to SoA Section 1.2 for specific time points and volumes for collection of samples.

Transcriptome studies may be conducted using RNA sequencing or comparable techniques, which facilitate the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response to vaccination.

Plasma and/or serum may be analyzed for soluble immune mediators by quantification using multiplex assays.

Samples will be stored according to local regulations at a facility selected by the sponsor.

Collected samples will be used for protocol related biomarker research. In addition, only with the explicit and optional consent of study participants, samples or partial sample volumes that remain once a protocol-defined assay has been completed, may be stored and used for purposes other than protocol-related endpoints. Such “future research studies” would include assay development, assay quality control and development of methods related to TB research and TB vaccine research, including studies that pertain to the improvement, development and quality

assurance of the lab tests described in this protocol. If future research must be conducted in countries other than RSA, a separate request for approval will be made to the IRB/IEC, informed consent/assent will be required, and is subject to laws and regulations of the RSA and to IRB/IEC approval.

8.8. Health Economics

Not applicable

9. Statistical Considerations

9.1. Statistical Hypotheses

There are no formal statistical hypotheses to support the objectives of this study.

9.2. Sample Size Determination

Safety

With N = 200 vaccinated with M72/AS01$_E$, there is at least 90% (80%) power to observe at least 1 AE if the true rate is at least 1.2% (0.8%). Therefore, there is high probability to observe at least 1 SAE, or 1 AESI if the true AE rate is relatively low (~1%).

M72 immunogenicity

The sample size is not driven by the immunogenicity endpoints. Table 6 provides the power to show statistically significant differences in GMCs between the two treatment groups for varying sample sizes when the true differences are between 10% and 40% higher in the vaccine arm, and the coefficient of variation (CV) of the measurement is between 30% and 50%.

Table 6: Statistically significant differences in geometric mean concentrations (GMCs) between the two treatment groups for varying sample sizes

N per group	CV	True geometric mean increase in vaccine arm			
		10%	20%	30%	40%
50	30%	36.0	87.4	99.4	> 99.9
	40%	23.0	65.1	92.0	99.1
	50%	16.3	48.2	78.7	94.4
100	30%	62.3	99.2	> 99.9	> 99.9
	40%	42.2	90.8	99.9	> 99.9
	50%	29.5	77.0	97.5	> 99.9
150	30%	80.3	> 99.9	> 99.9	> 99.9
	40%	56.6	98.1	> 99.9	> 99.9
	50%	41.5	90.9	99.8	> 99.9
200	30%	90.0	> 99.9	> 99.9	> 99.9
	40%	68.8	99.7	> 99.9	> 99.9
	50%	53.0	97.0	> 99.9	> 99.9

With N = 200 per group, there is excellent power (≥ 97%) to show statistically significant differences in GMCs between the two treatment groups when the true differences are at least

20% higher in the vaccine arm, and CV of the measurement is as high as 50%. The table clearly shows that sample sizes lower than 200 per group are likely sufficient to show meaningful differences in immunogenicity between the vaccine and placebo groups. While samples will be collected and stored at all planned immunogenicity timepoints, strategies to test only a portion of participants for immunogenicity analyses may be considered. Final plans will be documented in a separate statistical analysis plan (SAP) prior to data unblinding.

9.3. Populations for Analyses

Analysis populations are shown in Table 7.

Table 7: Populations for Analyses

Population	Description
Randomized	All participants randomly assigned to study intervention, a randomization number and date.
Safety	All participants randomly assigned to study intervention and who received the study intervention. Participants will be analyzed according to the intervention they actually received.
Intention to treat (ITT) population	All participants randomly assigned to study intervention and who received the study intervention. Participants will be analyzed according to the intervention they were randomized.
Modified intention to treat (mITT) population.	All participants randomly assigned to study intervention and who received the study intervention and who were randomly selected and tested for immunogenicity.. Participants will be analyzed according to the intervention they actually received.
Per Protocol (PP) population	All participants randomly assigned to study intervention, who received the study interventions as planned and did not substantially deviate from the protocol procedures. Participants who substantially deviated will be identified prior to database lock and unblinding. Participants will be analyzed according to the intervention they actually received.
Per-Protocol for Immunogenicity Population	All participants in PP population randomly selected to have immunogenicity assays performed.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe in further detail the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

Some exploratory analyses may be included in this SAP. Other exploratory endpoint analyses such as those centered on exploratory biomarker analyses, may be described in a separate exploratory scientific and statistical analysis plan (exploratory SAP). Specific objectives and hypotheses related to exploratory biomarker analyses will be documented in the exploratory SAP prior to full data unblinding and analysis. Results from the exploratory analyses may be reported in a separate results memo and included as an addendum to the clinical study report (CSR).

Analyses based on study endpoints are summarized in Table 8.

Table 8: Summary of Endpoints and Analyses

Primary Endpoint	**Statistical Analysis**
Solicited AEs through 7 days post each dose of study intervention Unsolicited AEs through 28 days post each dose of study intervention All SAEs through end of study	The incidence and 95% confidence intervals of AEs will be summarized by treatment group, overall, and by grade, intensity, and relatedness. The incidence and 95% confidence intervals of SAEs will be summarized by treatment group.
Secondary Endpoints	**Statistical Analysis**
pIMDs through end of study Safety laboratory assessments grade 3 or above through end of study	Summary statistics will be generated for pIMDs, laboratory safety tests including grade 3 and above.
M72-specific antibody titers at Day 1, Day 29, Day 57, Day 210 and Day 390	Anti-M72/AS01$_E$ seropositive rates and GMCs will be calculated by treatment and time point with exact 95% CIs.
Frequency and magnitude of M72-specific $CD4^+$ and $CD8^+$ T-cell responses measured by expression of IFN-γ or IL-2 by ICS at Day 1, Day 57 and Day 390	The frequency of $CD4^+$ T cells positive for IFN-γ or IL-2, by ICS, will be summarized by treatment group and timepoint. Median DMSO-subtracted cytokine responses and associated 95% CIs will be used to summarize percentage T cell responses.
Exploratory Endpoints	**Statistical Analysis**
Frequency and magnitude of M72-specific $CD4^+$ and $CD8^+$ T-cell responses measured by expression of IFN-γ or IL-2 by ICS at Day 29 and Day 210	The frequency of $CD4^+$ T cells positive for IFN-γ or IL-2, by ICS, will be summarized by treatment group and timepoint. Median DMSO-subtracted cytokine responses and associated 95% CIs will be used to summarize percentage T cell responses.

Exploratory Endpoints	Statistical Analysis
Polyfunctionality of M72-specific CD4+ and CD8+ T-cell responses measured by co-expression of multiple functional markers by ICS	Polyfunctionality will be analyzed by COMPASS*, and summarized by treatment group using functionality and/or polyfunctionality scores.
Frequencies of participants with confirmed HIV RNA >200 copies/mL at Day 57, Day 210 and Day 390	Frequencies of participants with confirmed HIV RNA will be summarized by treatment group and timepoint, with associated 95% CIs
Mean changes in $CD4^+$ T cell count from baseline to Day 57, Day 210 and Day 390	Mean changes in $CD4^+$ T cell count will be summarized based on timepoints from baseline
Suspected TB during the study	Summary statistics will be generated for the incidence of suspected TB by treatment group and timepoint.
Laboratory-confirmed pulmonary TB during the study	Summary statistics will be generated for the incidence of Laboratory-confirmed pulmonary TB by treatment group and timepoint.

* [Lin 2015]

Analyses for other exploratory endpoints may include, but are not limited to:

- assessing functional antibody profiles in response to vaccination
- vaccine-induced changes in innate and myeloid cell populations, and
- vaccine-induced changes in transcriptomic, proteomic or metabolomic profiles.

In addition to these analyses, any observed cases of TB disease will be summarized and described by treatment group.

9.4.1. Humoral Immunogenicity Analyses

Anti-M72/$AS01_E$ seropositive rates and GMCs will be calculated by treatment and time point with exact 95% CIs.

To formally compare GMCs between treatment groups, a linear mixed effect model will be used, including fixed effects for treatment and time, and a random effect for participant. Individual M72-specific IgG antibody titers will be log-transformed. GMCs and 95% CIs will be estimated from the model as the back-transformed mean estimate.

To formally compare seropositivity rates between treatment groups, a generalized linear mixed effect model will be used, including fixed effects for treatment and time, and generalized estimating equations will be used to account for the dependence in the longitudinal binomial response data.

Formal comparisons before and after study intervention (e.g., geometric mean ratios (GMR), differences in seropositivity rates) will be generated from the model results with 95% CIs.

9.4.2. Cell-mediated Immune response

Frequency, magnitude and polyfunctionality of M72-specific $CD4^+$ and $CD8^+$ T-cell responses measured by ICS before and following vaccination at specified time points through the end of the study with associated CIs will be summarized. Summaries of T-cell response will be presented by T-cell type ($CD4^+$ and $CD8^+$), functionality (cytokines expressed) and by stimulation antigen. Summaries will include immune responses at pre- and post-study intervention immunology time points, and change from pre-vaccination to post-vaccination time points.

Similar analysis methods will be used to compare cellular immune responses over time between treatment groups.

9.4.3. Exploratory analyses

Summary statistics will be generated for the incidence, by treatment group, of suspected TB disease and laboratory-confirmed pulmonary TB that occur throughout the study period.

Specific objectives related to additional exploratory immunogenicity and/or exploratory transcriptomic, proteomic and/or metabolomic assessments will be also be examined. Specific objectives and hypotheses related to these analyses will be documented and if not reported with the final CSR, will be reported separately, and described in the SAP prior to data unblinding and analysis.

9.4.4. Subgroup Analyses

The consistency of results with respect to the primary and secondary objectives will be examined within various subgroup populations (e.g., by QFT status, sites and maybe others). Details will be provided in the SAP.

9.4.5. Demographic and Compliance Analyses

Demographic parameters (age, sex, and race/ethnicity) and other baseline characteristics will be summarized by treatment group for all participants in the safety population.

Listings of randomized participants with protocol deviations (to be defined in the SAP) will be presented by treatment group.

9.5. Interim Analyses

Interim analyses are not planned.

9.5.1. Independent Data Monitoring Committee (IDMC)

The IDMC will operate according to a charter. The IDMC structure, participants and other details will be provided in the charter. The charter will be available prior to study start.

The IDMC will review unblinded safety data during regular scheduled safety review meetings as well as the outcome of the primary and secondary analyses. The IDMC may request additional information, or a pause in recruitment and vaccination, while safety data are being evaluated.

During active enrollment, the IDMC will meet approximately at least once every 3 months and ad hoc as necessary. The IDMC review will include solicited and unsolicited AEs, as well as SAEs, AESIs, and any safety laboratory measurements that are grade 3 and above. All procedures associated with this review, including objectives, data handling, and elements to be included for review will be documented.

The IDMC may request additional information, or a pause in recruitment and vaccination, while safety data are being evaluated. Refer to Section 7.4 for details. The IDMC will make a formal recommendation on the continued enrollment into the trial after each safety review.

The IDMC charter will provide meeting information and other details.

If study vaccine administration is paused by the Medical Monitor or the PI, the IDMC will convene ad hoc.

The recommendations of the IDMC, along with the sponsor's decision, will be communicated to the investigators and the IRBs/IECs and the national regulatory authorities as required. The sponsor or its designee agrees to abide by any directives issued by the national regulatory authority or the IRB/IEC.

9.5.2. Informed Consent and Assent Process

The PI or his or her representative will explain the study to the participant and, for participants who are minors, to his or her parent or guardian/LAR, and answer all questions regarding the study. The PI or designee will conduct the consent and assent discussions on an individual basis with each participant and parent or guardian/LAR. Adequate time will be allowed for all questions to be addressed. Potential participants will be interviewed to ensure that they meet all entry criteria relating to history.

Participants must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent (ICF) that meets the requirements of FDA Code of Regulations (CFR) 21 CFR 50, local regulations, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and the IRB/IEC or study center.

Participants who are under the age of informed consent (less than 18 years of age) must sign an informed assent form (IAF) and their parent or guardian/LAR must sign an ICF prior to enrollment.

The CRF must indicate that written informed consent or assent was obtained before the participant was enrolled in the study and the date the written consent or assent was obtained. The authorized person obtaining the informed consent or assent must also sign the ICF.

Participants must be re-consented/assented to the most current version of the ICF(s) during their participation in the study, and any participant who previously signed an IAF, and then reaches the age of consent during the study, must sign a consent form at the next scheduled study visit.

A copy of the ICF or IAF must be provided to the participant or guardian/LAR.

9.5.2.1. Informed Consent forms

Informed consent for study participation

If a participant cannot be randomized on the intended day of vaccination (e.g., if elevated temperature) her/she is not required to sign another ICF/IAF (as applicable), as long as re-screening and vaccination occur within the protocol-defined window.

The ICF and IAF contain a separate section that addresses the use of remaining mandatory samples for research not described in the protocol, e.g., assay development and assay quality control. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for research not described in the protocol.

Participants will be told that they are free to refuse to participate and may withdraw their consent or assent at any time and for any reason during the storage period. Participants will also be informed that laboratory tests will be run in laboratories in and outside of the RSA.

9.5.3. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant record or dataset that is transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the sponsor.

The participant must be informed that his or her study-related data will be used by the sponsor in accordance with local data protection law. The level of data disclosure must also be explained to the participant.

The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.5.4. Dissemination of Clinical Study Data

Study information from this protocol will be posted on publicly available clinical trials registers (clinicaltrials.gov and the RSA registry [sanctr.gov.za]) before enrollment of participants begins. Summaries of the results of the study will also be posted on the same website.

The final CSR will include all available safety data, immunogenicity data, clinical assessments, and concomitant medications through the final study visit. The database will be locked prior to preparation of the final CSR when all of the above data have been entered, reviewed, and all queries related to the data have been addressed. Modifications or additions to the analyses will be included in the relevant SAP. Any decisions to deviate from the planned analyses described in the protocol and in the SAP will be described in detail in the final CSR. The CSR will be reviewed and approved by the sponsor signatory and the lead PI.

9.5.5. Data Quality Assurance

All participant data relating to the study will be recorded on a printed CRF or, by an electronic CRF using an Electronic Data Capture (EDC) system, unless transmitted to the sponsor or

designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically signing or electronically signing the CRF.

The investigator must maintain accurate documentation that supports the information entered in the CRF.

The study will be monitored regularly by the sponsor or its designee throughout the study period. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs and IAFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

9.5.6. Source Documents

Source documentation consists of existing medical records and/or study records developed and maintained by the investigator. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Diary card and memory aid are source documents.

Data recorded on source documents will be transcribed onto CRFs either paper, or electronically using an EDC system.

Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.

9.5.7. Study and Site Closure

The sponsor designee reserves the right to close the study site(s) or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

9.5.8. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 1

9.6. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

9.6.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiography [ECG], radiological scans, vital signs), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present (date of first sign or symptom) before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.6.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.6.3. Definition of SUSAR

SUSARs are defined as any *unexpected* AEs that are *serious* and *suspected of being related* to the study intervention (suspected adverse drug reactions). See Section 9.6.5.3 regarding expectedness.

9.6.4. Definition of AESI

Adverse events of special interest (AESIs) are adverse events that the sponsor wants to monitor carefully. The following list, which includes pIMDs, will be collected and reported as AESIs. Refer to Section 9.6.7 for the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) codes.

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy, - Multifocal motor neuropathy - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: - Diffuse Scleroderma - CREST syndrome • Idiopathic inflammatory myopathies, including: - Dermatomyositis - Polymyositis • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: - Juvenile Idiopathic Arthritis - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing Spondylitis, - Reactive Arthritis (Reiter's Syndrome), - Undifferentiated Spondyloarthritis, - Psoriatic Arthritis, - Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localised Scleroderma (Morphoea).

Vasculitis	Blood disorders	Others
• Large vessels vasculitis including: - Giant Cell Arteritis (Temporal Arteritis), - Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: - Polyarteritis nodosa, - Kawasaki's disease, - Microscopic Polyangiitis, - Wegener's Granulomatosis (granulomatosis with polyangiitis), - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), - Buerger's disease (thromboangiitis obliterans), - Necrotizing vasculitis (cutaneous or systemic), - anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), - Henoch-Schonlein purpura (IgA vasculitis), - Behcet's syndrome, - Leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: - IgA nephropathy, - Glomerulonephritis rapidly progressive, - Membranous glomerulonephritis, - Membranoproliferative glomerulonephritis, - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: - Autoimmune uveitis - Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory Bowel disease, including: - Crohn's disease, - Ulcerative colitis, - Microscopic colitis, - Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type I. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

9.6.5. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- AEs will be reported on the AE CRF using a recognized medical term or diagnosis that accurately reflects the event.
- AE evaluations will be reviewed by the PI or a medically qualified delegate. AE CRF pages are to be completed by members of the study team designated in writing by the PI. The onset and resolution dates of an AE and action taken in response to the AE will be documented.
- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Medical Monitor, the IDMC or the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- SAEs will be assessed for intensity and causal relationship to the study intervention.

Follow-up of AEs and SAEs/AESI and Resolution

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of receipt of the information.
- The onset and resolution dates of the event and medical care taken in response to the event will be documented.
- AEs will be considered resolved when the condition returns to normal or returns to the participant's baseline status as established on Study Day 1, or when the condition has stabilized with the expectation that it will remain chronic.
- If the event has not resolved by the final study visit, it will be documented as "ongoing" on the CRF, however, follow-up of the SAE must continue until resolved or the condition has stabilized. Information recorded on the CRF must be substantiated in the source documents.
- The resolution date to be recorded on the CRF is the last date on which the participant experienced the AE.

9.6.5.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of 4 categories:

- **Mild** symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
- **Moderate** symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
- **Severe** symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated
- **Potentially life-threatening** symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

9.6.5.2. Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- An AE/SAE is considered related to study intervention if there is a reasonable possibility that the study intervention contributed to the AE.
- Not-related means there is no reasonable possibility that the AE is causally related to administration of the study intervention. There are other more likely causes for the AE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always makes an assessment of causality before the initial transmission of the SAE data.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.6.5.3. Assessment of Expectedness of SAEs

Expectedness assessment of SAEs is done by the sponsor using the applicable reference safety information for reportability purposes.

9.6.5.4. Assessment of Outcome

The outcome of each SAE must be reported to the sponsor. For analysis purposes, the outcome for serious adverse events will be determined on the final study visit.

Outcome of all AEs will be classified as one of the following:

•Resolved

•Resolved with sequelae

•Ongoing

•Death.

9.6.6. SAEs and AESIs Reporting

Reporting to sponsor delegate's (CRO Safety Team) via the Electronic Data Collection Tool

- The primary mechanism for reporting an SAE, or AESI by the investigator to the sponsor or delegate will be the electronic data collection tool.

- The site will enter the SAE or AESI data into the electronic system as soon as it is identified.
- All SAEs and AESIs are reported to the sponsor and to the CRO Safety team throughout the 12 months after study intervention administration.
- The investigator must not wait to collect additional information to fully document the event before notifying the CRO Safety team of an SAE, or AESI. The initial notification should include the following:
    - Protocol number and name and contact number of the investigator
    - Participant ID number (and initials and date of birth, if available)
    - Date participant received study vaccine
    - Term and date of event onset
    - Current status of event
- The investigator is responsible for expedited safety report submission to the Sponsor delegate and the Sponsor delegate for reporting to SAHPRA within specific time periods of being notified of the event. Therefore, it is important that the investigator submit additional information requested as soon as it becomes available. The sponsor is responsible for the determination of the expectedness according to the reference safety information section of the applicable investigator's brochure.
- All fatal and life-threatening adverse drug reactions and SUSARs are to be reported to SAHPRA with 7 calendar days after first knowledge with a complete report to be submitted within an additional 8 calendar days. SUSARs that are not fatal or life threatening need to be reported to SAHPRA no later than 15 calendar days after first knowledge. The sponsor will notify the IDMC of all SUSARs within the same timelines the report is sent to investigators, health authorities, and other relevant parties. Any follow-up report will be sent with the same timelines. The principal investigator is responsible for the notification of such reports to the applicable IRB/IEC.
- If the electronic system is unavailable, the site may use the paper SAE data collection tool (see next section) instead of the EDC, in order to report the event within 24 hours of becoming aware.
- After the study is completed at a given site, the electronic data collection tool, if used, will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).

- Contacts for SAE reporting and for all safety personnel are contained in the Team Contact List which will be stored on site in the Site Regulatory Binder and maintained by the study sponsor.

SAE Reporting via Paper CRF

- If the CRF cannot be completed, the Supplemental SAE Report (paper form) should be completed by the PI or his/her designee, and scanned and emailed, or faxed to the CRO Safety Team. The investigator is responsible for ensuring an adequate transmission of the fax and will store the distribution confirmation in the study file.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE report form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Other Events Requiring Immediate Reporting

- The investigator must report the following events by scanning and emailing, or faxing the appropriate form to the CRO Safety Team within 24 hours of becoming aware of the event:
- Withdrawal of consent during the study for medical reasons (Immediately Reportable Event Form)
- Emergency unblinding (Immediately Reportable Event Form)
- Protocol violation affecting the safety of a participant or involving the vaccination process (Immediately Reportable Event Form)
- Any event that, in the opinion of the investigator, precludes further administration of the study vaccine (Immediately Reportable Event Form, unless meets SAE criteria)
- Pregnancy (Immediately Reportable Event Form, and Pregnancy Notification Form which may be included in the CRF)

9.6.7. Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 Preferred Term Codes for pIMDs

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
Neuroinflammatory disorders	Cranial nerve disorders and inflammations	Anosmia	10002653
		IIIrd nerve paralysis	10021283
		IIIrd nerve paresis	10054202
		IVth nerve paralysis	10023110
		IVth nerve paresis	10054201
		Trigeminal palsy	10049788
		Trigeminal nerve paresis	10068008
		Vlth nerve paralysis	10047641
		Vlth nerve paresis	10071044
		Facial paralysis	10016062
		Facial paresis	10051267
		Acoustic neuritis	10063162
		Glossopharyngeal nerve paralysis	10051270
		Tongue paralysis	10043972
		Vagus nerve paralysis	10064661
		Vocal cord paralysis	10047674
		Vocal cord paresis	10049234
		XIth nerve paralysis	10048842
		Hypoglossal nerve paralysis	10069450
		Hypoglossal nerve paresis	10067129
		Bulbar palsy	10006542
		Oculofacial paralysis	10030069
		Neuritis cranial	10029244
		Cranial nerve disorder	10061093
		Paresis cranial nerve	10061911
		Cranial nerve paralysis	10061908
		Cranial nerve palsies multiple	10011314
		Optic neuritis	10030942
	Multiple sclerosis	Multiple sclerosis	10028245
		Radiologically isolated syndrome	10079292
		Primary progressive multiple sclerosis	10063401
		Progressive multiple sclerosis	10053395
		Marburg's variant multiple sclerosis	10067067
		Secondary progressive multiple sclerosis	10063400
		Multiple sclerosis relapse	10048393
		Relapsing multiple sclerosis	10080700
		Multiple sclerosis relapse prophylaxis	10070495
		Progressive relapsing multiple sclerosis	10067063
		Relapsing-remitting multiple sclerosis	10063399
		Tumefactive multiple sclerosis	10078556
		Expanded disability status scale score decreased	10071385
		Expanded disability status scale score increased	10071384
	Myelitis / Transverse myelitis	Myelitis transverse	10028527
		Myelitis	10028524
		Acute flaccid myelitis	10082097
		Noninfectious myelitis	10071764
	Guillain-Barré syndrome	Guillain-Barré syndrome	10018767
		Miller Fisher syndrome	10049567
	Acute disseminated encephalomyelitis and demyelination (including site specific variants)	Demyelination	10012305
		Intramyelinic oedema	10083038
		Autoimmune demyelinating disease	10075688
		Clinically isolated syndrome	10071068

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
		Leukoencephalomyelitis	10048999
		Leukoencephalopathy	10024382
		Acute disseminated encephalomyelitis	10000709
		Acute haemorrhagic leukoencephalitis	10058994
		Concentric sclerosis	10010252
		Encephalitis periaxialis diffusa	10049020
		Limbic encephalitis	10078012
		Neuromyelitis optica spectrum disorder	10077875
		Neuromyelitis optica pseudo relapse	10080353
		Autoimmune encephalopathy	10075691
		Bickerstaff's encephalitis	10076985
		Noninfective encephalitis	10074712
		Encephalitis autoimmune	10072378
		Immune-mediated encephalitis	10083074
		Rasmussen encephalitis	10071141
		Encephalitis allergic	10056387
		Encephalitis brain stem	10048997
		Encephalitis haemorrhagic	10014589
		Encephalomyelitis	10014619
		Noninfective encephalomyelitis	10074713
		Encephalitis post immunisation	10014602
		Panencephalitis	10056332
		Encephalitis toxic	10014607
		Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	10075210
	Myasthenia gravis	Myasthenia gravis	10028417
		Myasthenia gravis crisis	10062758
		Ocular myasthenia	10049168
		Myasthenic Syndrome	10028424
	Autoimmune / Immune-mediated peripheral neuropathies and plexopathies	Autoimmune neuropathy	10070439
		Immune-mediated neuropathy	10078963
		Neuritis	10029240
		Anti-myelin-associated glycoprotein associated polyneuropathy	10078324
		Subacute inflammatory demyelinating polyneuropathy	10081726
		Chronic inflammatory demyelinating polyradiculoneuropathy	10057645
		Lewis-Sumner syndrome	10065580
		Demyelinating polyneuropathy	10061811
		Polyneuropathy idiopathic progressive	10036111
		Multifocal motor neuropathy	10065579
		Acute motor-sensory axonal neuropathy	10076657
		Acute motor axonal neuropathy	10076658
		Cervical neuritis	10008293
		Mononeuritis	10027910
		Mononeuropathy multiplex	10027918
		Brachial plexopathy	10065417
		Radiculitis brachial	10037778
		Neuralgic amyotrophy	10029229

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
	Narcolepsy	Narcolepsy	10028713
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus	10042945
		SLE arthritis	10040968
		Cutaneous lupus erythematosus	10056509
		Acute cutaneous lupus erythematosus	10057928
		Chronic cutaneous lupus erythematosus	10057929
		Subacute cutaneous lupus erythematosus	10057903
		Lupus cystitis	10074714
		Lupus encephalitis	10025130
		Lupus endocarditis	10058225
		Lupus enteritis	10067738
		Lupus hepatitis	10067737
		Lupus myocarditis	10066391
		Lupus myositis	10079642
		Lupus nephritis	10025140
		Lupus pancreatitis	10067750
		Lupus pleurisy	10073694
		Lupus pneumonitis	10057481
		Lupus-like syndrome	10050551
		Neuropsychiatric lupus	10063663
		Central nervous system lupus	10076328
		Pericarditis lupus	10058149
		Peritonitis lupus	10062898
		Systemic lupus erythematosus rash	10042946
		Systemic lupus erythematosus disease activity index abnormal	10067659
		Systemic lupus erythematosus disease activity index decreased	10067658
		Systemic lupus erythematosus disease activity index increased	10067657
	Systemic Scleroderma (Systemic sclerosis)	Scleroderma	10039710
		Scleroderma renal crisis	10062553
		Scleroderma associated digital ulcer	10073229
		Reynold's syndrome	10070953
		Systemic sclerosis pulmonary	10042954
		Systemic scleroderma	10078638
		Anti-RNA polymerase III antibody increased	10082280
		Anti-RNA polymerase III antibody positive	10082283
		CREST syndrome	10011380
	Muscular Autoimmune / Immune-mediated disorders	Polymyalgia rheumatica	10036099
		Dermatomyositis	10012503
		Polymyositis	10036102
		Autoimmune myositis	10082418
		Immune-mediated myositis	10083073
		Juvenile polymyositis	10076673
		Antisynthetase syndrome	10068801
	Rheumatoid arthritis and associated conditions	Rheumatoid arthritis	10039073
		Autoimmune arthritis	10071155
		Immune-mediated arthritis	10083155
		Laryngeal rheumatoid arthritis	10059669
		Rheumatoid lung	10039081
		Rheumatoid scleritis	10067427
		Rheumatic brain disease	10079411
		Rheumatoid neutrophilic dermatosis	10072362

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
		Rheumatoid nodule	10048694
		Juvenile idiopathic arthritis	10059176
		Cogan's syndrome	10056667
		Palindromic rheumatism	10033534
		Still's disease	10042061
	Spondyloarthropathies	Arthritis reactive	10003267
		Reiter's syndrome	10038294
		Ankylosing spondylitis	10002556
		Spondylitis	10061371
		Spondyloarthropathy	10051265
		Juvenile spondyloarthritis	10076675
		Enteropathic spondylitis	10076549
		Psoriatic arthropathy	10037162
		Juvenile psoriatic arthritis	10076674
	Relapsing polychondritis	Polychondritis	10065159
	Mixed connective tissue disease	Overlap syndrome	10068786
		Mixed connective tissue disease	10027754
	Gout	Gout	10018627
		Gouty arthritis	10018634
		Gouty tophus	10018641
Gastrointestinal disorders	Inflammatory Bowel disease	Crohn's disease	10011401
		Colitis ulcerative	10009900
		Colitis microscopic	10056979
		Autoimmune colitis	10075761
		Immune-mediated enterocolitis	10078961
		Inflammatory bowel disease	10022102
		Arthritis enteropathic	10003253
		Proctitis ulcerative	10036783
		Autoimmune enteropathy	10081456
	Autoimmune / Immune-mediated pancreatitis	Autoimmune pancreatitis	10069002
		Immune-mediated pancreatitis	10083072
	Celiac disease	Coeliac disease	10009839
Liver disorders	Autoimmune / Immune-mediated hepatobiliary diseases	Autoimmune hepatitis	10003827
		Immune-mediated hepatitis	10078962
		Biliary cirrhosis primary	10004661
		Primary biliary cholangitis	10080429
		Cholangitis sclerosing	10008609
Endocrine and Metabolic disorders	Autoimmune / immune-mediated thyroid diseases	Autoimmune hypothyroidism	10076644
		Immune-mediated hypothyroidism	10083075
		Atrophic thyroiditis	10077172
		Autoimmune thyroiditis	10049046
		Immune-mediated thyroiditis	10083071
		Silent thyroiditis	10079012
		Hashimoto's encephalopathy	10069432
		Hashitoxicosis	10067873
		Basedow's disease	10004161
		Marine Lenhart syndrome	10068828
		Autoimmune thyroid disorder	10079165
	Autoimmune / Immune-mediated endocrinopathy (NOS)	Autoimmune endocrine disorder	10078953
		Immune-mediated endocrinopathy	10078964
	Diabetes mellitus type I	Type 1 diabetes mellitus	10067584
		Fulminant type 1 diabetes mellitus	10072628
	Polyglandular autoimmune syndrome	Polyglandular autoimmune syndrome type I	10036072
		Polyglandular autoimmune syndrome type II	10036073
		Polyglandular autoimmune syndrome type III	10064115
	Autoimmune hypophysitis	Lymphocytic hypophysitis	10063685

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
	Addison's disease	Addison's disease	10001130
Skin disorders	Psoriasis	Psoriasis	10037153
	Vitiligo	Vitiligo	10047642
	Erythema nodosum	Erythema nodosum	10015226
	Alopecia areata	Alopecia areata	10001761
	Lichen planus	Lichen planopilaris	10081142
		Lichen planus	10024429
	Sweet's syndrome	Acute febrile neutrophilic dermatosis	10000748
	Autoimmune / Immune-mediated bullous skin diseases	Pemphigus	10034280
		Pemphigoid	10034277
		Dermatitis herpetiformis	10012468
		Autoimmune dermatitis	10075689
		Immune-mediated dermatitis	10083156
	Localised Scleroderma	Morphoea	10027982
Vasculitides	Vasculitis and vasculitides	Acute haemorrhagic oedema of infancy	10070599
		Administration site vasculitis	10075969
		Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894
		Aortitis	10002921
		Application site vasculitis	10076027
		Arteritis	10003230
		Arteritis coronary	10003232
		Behcet's syndrome	10004213
		Capillaritis	10068406
		Central nervous system vasculitis	10081778
		Cerebral arteritis	10008087
		Chronic pigmented purpura	10072726
		Cutaneous vasculitis	10011686
		Diffuse vasculitis	10012978
		Eosinophilic granulomatosis with polyangiitis	10078117
		Erythema induratum	10015213
		Granulomatosis with polyangiitis	10072579
		Haemorrhagic vasculitis	10071252
		Henoch-Schonlein purpura	10019617
		Henoch-Schonlein purpura nephritis	10069440
		Hypersensitivity vasculitis	10020764
		Injection site vasculitis	10067995
		Kawasaki's disease	10023320
		Langerhans' cell histiocytosis	10069698
		Lupus vasculitis	10058143
		MAGIC syndrome	10078132
		Microscopic polyangiitis	10063344
		Nodular vasculitis	10029491
		Ocular vasculitis	10066926
		Optic ischaemic neuropathy	10030924
		Optic neuropathy	10061323
		Polyarteritis nodosa	10036024
		Pulmonary vasculitis	10037457
		Renal arteritis	10038373
		Renal vasculitis	10038546
		Retinal vasculitis	10038905
		Rheumatoid vasculitis	10048628
		Segmented hyalinising vasculitis	10067527
		Takayasu's arteritis	10043097
		Temporal arteritis	10043207
		Thromboangiitis obliterans	10043540

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
		Urticarial vasculitis	10048820
		Vaccination site vasculitis	10076191
		Vascular purpura	10047097
		Vasculitic rash	10047111
		Vasculitic ulcer	10075714
		Vasculitis	10047115
		Vasculitis gastrointestinal	10048319
		Vasculitis necrotising	10047124
Other	Stevens-Johnson syndrome	Stevens-Johnson syndrome	10042033
		Erythema multiforme	10015218
		Toxic epidermal necrolysis	10044223
		SJS-TEN overlap	10083164
	Blood autoimmune / immune-mediated disoders	Autoimmune anaemia	10080243
		Autoimmune haemolytic anaemia	10073785
		Warm type haemolytic anaemia	10047822
		Cold type haemolytic anaemia	10009868
		Coombs positive haemolytic anaemia	10010941
		Evans syndrome	10053873
		Immune thrombocytopenic purpura	10074667
		Thrombocytopenic purpura	10043561
		Thrombotic thrombocytopenic purpura	10043648
		Autoimmune aplastic anaemia	10071576
		Autoimmune neutropenia	10055128
		Autoimmune pancytopenia	10069509
		Immune-mediated pancytopenia	10083004
		Antiphospholipid syndrome	10002817
		Pernicious anaemia	10034695
	Autoimmune / immune-mediated glomerulonephritis	Glomerulonephritis rapidly progressive	10018378
		IgA nephropathy	10021263
		IgM nephropathy	10077209
		C1q nephropathy	10081461
		Glomerulonephritis membranous	10018372
		Glomerulonephritis membranoproliferative	10018370
		Membranous-like glomerulopathy with masked IgG-kappa deposits	10083098
		Mesangioproliferative glomerulonephritis	10066453
		Anti-glomerular basement membrane disease	10081981
		Autoimmune nephritis	10077087
		Immune-mediated nephritis	10083070
		Chronic autoimmune glomerulonephritis	10073016
		Tubulointerstitial nephritis and uveitis syndrome	10069034
	Ocular autoimmune / immune-mediated diseases	Uveitis	10046851
		Vogt-Koyanagi-Harada disease	10082001
		Ocular pemphigoid	10067776
		Autoimmune retinopathy	10071578
		Acute macular outer retinopathy	10079367
		Autoimmune uveitis	10075690
		Immune-mediated uveitis	10083069
		Autoimmune eye disorder	10081123
	Autoimmune / immune-mediated heart disease	Autoimmune myocarditis	10064539
		Immune-mediated myocarditis	10082606
		Autoimmune pericarditis	10079058
	Sarcoidosis	Sarcoidosis	10039486
		Pulmonary sarcoidosis	10037430
		Neurosarcoidosis	10078011

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
		Cutaneous sarcoidosis	10011674
		Liver sarcoidosis	10068664
		Muscular sarcoidosis	10028390
		Ocular sarcoidosis	10065700
	Sjögren's syndrome	Sjogren's syndrome	10040767
	Autoimmune lung disease	Idiopathic pulmonary fibrosis	10021240
		Idiopathic interstitial pneumonia	10078268
		Interstitial lung disease	10022611
		Pulmonary fibrosis	10037383
		Autoimmune lung disease	10080701
		Immune-mediated pneumonitis	10082452
	Goodpasture's syndrome	Goodpasture's syndrome	10018620
	Raynaud's phenomenon	Raynaud's phenomenon	10037912

Appendix 2

9.7. Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Female of Childbearing Potential (FOCBP)
A female is considered fertile following menarche. If fertility is uncertain (e.g., amenorrhea in adolescents) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered. If in doubt, the participant should be considered fertile.

Women in the following categories are not considered FOCBP

1. Premenarchal
2. Documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

Women physically capable of pregnancy must agree to use an acceptable method of avoiding pregnancy **for one year after the start of study intervention**.

Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label.

Effective methods include contraceptive intrauterine device or system, subdermal contraceptive implant, progestogen injections, progestogen only oral contraceptive pills, combined estrogen and progestogen oral contraceptive pills, percutaneous contraceptive patch, and contraceptive vaginal ring.

Routinely counsel females to use condoms for dual protection against pregnancy and to avoid transmission of HIV and other sexually transmitted infections at all scheduled study visits.

Adequate contraception does not apply to participants of child-bearing potential with same sex partners, when this is their preferred and usual lifestyle.

Collection and Reporting Pregnancy Information

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

- The health status of the mother and child, the date of delivery, and the child's sex, birth weight and multiparity should be recorded and be reported to the Medical Monitor after delivery. If delivery occurs before the last scheduled study visit, the participant should continue to be followed to determine the outcome of the pregnancy, and for SAEs through the final study visit unless withdrawal of consent has occurred. If delivery occurs after the final study visit, the investigator should attempt to maintain contact with the participant to obtain information after delivery.
- The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Any post-study pregnancy-related SAE considered related to the study intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Appendix 3

9.8. Toxicity Table

Modified from Division of AIDS Table for Grading the Intensity (severity) of Adult and Pediatric Adverse Events Version 2.1, July 2017

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
ESTIMATING INTENSITY GRADE				
Clinical adverse event NOT identified elsewhere in the Grading Table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities, with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions, with intervention indicated to prevent permanent impairment, persistent disability, or death

Cardiovascular

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and sex (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and sex (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Cardiac Ischemia or Infarction *Report only one*	Not applicable (NA)	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g.,oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval [2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

[2] As per Bazett's formula.

Dermatologic

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus [1] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[1] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

Endocrine and Metabolic

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social &	Symptoms causing inability to perform usual social & functional activities OR	Life-threatening consequences (e.g., myxedema coma)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
		functional activities OR Thyroid replacement therapy indicated	Uncontrolled despite treatment modification	
Lipoatrophy[1]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[2]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[1] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

[2] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24- hr period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy Pseudo-membranes or ulcerations	Confluent pseudo-membranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure,

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
				hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[1] *< 30 years of age*	BMD z-score -2 to -1	NA	NA	NA

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
≥ 30 years of age	BMD t-score -2.5 to -1	NA	NA	NA
Osteoporosis[1] *< 30 years of age*	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
≥ 30 years of age	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[1] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a fulltime basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or preexisting febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to <20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., statusser epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., intensity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[1] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[1] A pregnancy loss occurring at < 20 weeks gestational age

Psychiatric

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or panuveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social &	Visual changes causing greater than minimal interference with usual social	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
	functional activities	& functional activities		

Systemic

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[1]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥ 38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to < 40.0°C or ≥ 102.7 to <104.0°F	≥40.0°C or ≥104.0°F
Pain[2] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[3]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[4] *>5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[1] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[2] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

[3] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[4] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs:

http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age

Urinary

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[1] *Report only one > 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter or ≥ < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Injection Site Induration or Swelling *Report only one > 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[1] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values*

Chemistries

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Acidosis	NA	pH ≥ 7.3 to < Lower limit of normal (LLN)	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x upper limit of normal (ULN)	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[1], High > 28 days of age***	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[1] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 ≥ 3.38
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Creatinine Clearance[1] or eGFR, Low **Report only one*	NA	< 90 to 60 mL/min or mL/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 mL/min or mL/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 mL/min or mL/min/1.73 m^2 OR ≥ decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium [2], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) *> 14 years of age*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L;*mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L;*mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

[1] Creatinine clearance- Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

[2] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Hematology

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[1], Low (g/dL; *mmol/L*)[2] *≥ 13 years of age (male)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (%hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*

[1] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[2] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory

Urinalysis

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

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11. Amendment History

Rationale for Version 3 dated *final draft* 02 February 2021

Protocol Version 2.0 dated 01 May 2020 was the first version to be approved by SAHPRA and the Ethics Committee and used by the sites. First screening visit was on 09 Nov 2020 with the first randomization/dosing on 17 Nov 2020.

Protocol Version 3.0 is the first amendment to the protocol after study start. Version 3 was prepared to reflect that assays for secondary and exploratory endpoints will be carried out in laboratories outside of the RSA. These assays were originally intended to be performed in the RSA. For cellular responses, the sponsor was not able to identify a vendor who was able to consistently provide the services needed (18 color flow cytometry under Good Clinical Laboratory Practice [GCLP] conditions) in the RSA. For humoral responses, the laboratory was chosen in order to provide continuity with the assay used for previous studies, and that laboratory has provided the ELISA data for most of the previous M72 studies, in addition to having the most experience with the assay. Because of this, the informed consent and informed assent forms were also amended, and participants already enrolled will be reconsented.

Clinical data were being collected for TB disease but there was no Sputum Xpert MTB/RIF assay to confirm the case and there was no objective to describe the incidence so Xpert MTB/RIF assay for suspected TB and a corresponding objective was added. Timepoints to assess the CD4+ and CD8+ T cell responses were split into secondary and exploratory endpoints.

Following the secondary endpoints analyses, if responses at peak or memory are lower than expected compared to historical data from previous M72 vaccine studies, additional timepoints may be assessed as exploratory analysis to further characterize the kinetics of the cellular vaccine-induced immune response. Polyfunctionality of M72-specific $CD4^+$ and $CD8^+$ T-cell responses was moved from secondary to exploratory endpoint to support the exploratory cellular immunogenicity objective.

Other changes were made in response to site's request for clarity, or to correct an error.

A detailed summary of changes from Version 2 to Version 3 are listed below.

Header change: Version ~~2~~ ***3***

Footer change: ~~01 May 2020~~ to final draft 02 February 2021

Title page: Legal Registered Address:
One Kendall Square
Building 600, Suite 6-301
Cambridge, MA 02139
~~245 Main Street, Cambridge, MA 02142~~

Approval Date: ~~01 May 2020~~ *final draft 02 February 2021*

Page 2 sponsor signatory: ***Version 3*** **Sponsor Signatory**

[redacted] Clinical Development Leader

Table 1 and Table 3: Objectives and Endpoints

Objectives	Endpoints
Secondary	
• To assess the safety of M72/AS01$_E$ vaccination	• Potential immune-mediated diseases (pIMDs) through end of study • Safety laboratory assessments grade 3 or above through end of study
• To assess the humoral immunogenicity of M72/AS01$_E$ vaccination	• M72-specific antibody ***titers*** ~~concentrations pre- and post-vaccination through the end of the study~~ ***at Day 1, Day 29, Day 57, Day 210 and Day 390***
• To assess the cellular immunogenicity of M72/AS01$_E$ vaccination	• Frequency, ***and*** magnitude ~~and polyfunctionality~~ of M72-specific CD4~~*~~$^+$ and CD8$^+$ T-cell responses measured by ***expression of IFN-γ or IL-2 using*** intracellular cytokine staining (ICS) ~~pre- and post-vaccination through the end of the study~~ ***at Day 1, Day 57 and Day 390***
Exploratory	
• ***To further explore cellular immunogenicity of M72/AS01$_E$ vaccination***	• ***Frequency and magnitude of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by expression of IFN-γ or IL-2 by ICS at Day 29 and Day 210*** • ***Polyfunctionality of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by co-expression of multiple functional markers by ICS***
• To assess HIV viral load post-M72/AS01$_E$ vaccination	• Frequencies of participants with confirmed HIV ribonucleic acid ([RNA]>200 copies/mL) at Day 57, Day 210 and Day 390
• To assess changes in CD4$^+$ T cell count from baseline	• Mean changes in CD4$^+$ T cell count from baseline to Day 57, Day 210 and Day 390
• ***To describe the incidence of suspected TB disease and laboratory-confirmed pulmonary TB disease***	• ***Suspected TB during the study*** • ***Laboratory-confirmed pulmonary TB during the study***
Other exploratory endpoints may include, but are not limited to, assessing functional antibody profiles in response to vaccination, vaccine-induced changes in innate and myeloid cell populations, and vaccine-induced changes in transcriptomic, proteomic or metabolomic profiles.	

(note that the * was deleted from table and here) ~~*~~CD= cluster of differentiation

Throughout: corrected ie to i.e. and eg to e.g.

Synopsis and Section 4.1

Masking: ~~Site staff preparing and administering study interventions, including the pharmacist, will be unblinded but will not perform other study duties.~~ The i***nvestigational pharmacist preparing study interventions will be unblinded but will not perform other study duties.***

In Section 4.1, added: ***Refer to Section 6.2.2.***

Randomization: added comma after status (QFT) status***,*** based on results at screening.

Total duration of study participation: The study duration for each participant, ***after screening,*** is approximately 390 days, which includes ~~a maximum of 30 days for screening~~ 2 vaccinations, 1 month apart, and 365 days of follow-up post dose 2.

In Synopsis: ***Study sites***: ***Approximately 6*** ~~Up to five~~ sites in the ***Republic of South Africa (***RSA***)*** will participate in this study.

In Section 4.1: ~~Up to five~~ ***Approximately 6*** sites in the RSA…

Synopsis only: ***Schema: The screening visit will begin with the informed consent process.***

~~Once informed consent (and if necessary, informed assent) have been obtained, the screening visit will occur.~~

Table 2: Schedule of Activities (SoA)

Procedure	Screen	Intervention and Follow-up Period							
		Visit 1 Day 1	Visit 2 Day 8	Visit 3 Day 29	Visit 4 Day 36	Visit 5 Day 57	Visit 6 Day 210	Visit 7 Day 390	Discon Visit
Visit window	-30 to Day 0	±0	Day 8 to 12	Day 29 to 35	Day 36 to ***42*** ~~40~~	Day 57 to 63	±28days	±28days	
Full medical history/full physical examination (PE)***, height***	X								
Record Body weight, ~~(and height only at screening)~~ ***and pregnancy status***	X	X	X	X	X	X	X	X	X
Urine pregnancy test (prior to study ***intervention*** ~~product~~ admin***istration***)		X		X					
Urinalysis ***by dipstick*** (glucose, protein, blood), ***and microscopy***	X								
Sputum Xpert MTB/RIF assay ~~on a single self-expectorated sputum sample~~	X								
Sputum Xpert MTB/RIF assay ONLY if TB is suspected		***X***	***X***	***X***	***X***	***X***	***X***	***X***	***X***
M72-specific $CD4^+$ and $CD8^+$ T cells ~~(acid citrate dextrose tube)~~ (17 mL)		X		X		X	X	X	X
Exploratory CoP & CoR transcriptomics ***(***2.5 mL***)*** ~~(Paxgene tube)~~		X			X		X	X	X

Unsol. AE= unsolicited adverse event, conmed= concomitant medication
QFT= QuantiFERON®-TB Gold Plus assay (note that participants with an indeterminate result will not be eligible).
A single self-~~exporated~~***expectorated*** sputum ***sample*** will be collected for Xpert MTB/RIF assay ***from all participants at screening visit, and in participants with suspected TB at the other visits***. No sputum induction is required. Sputum Xpert MTB/RIF assay will not be done in participants who are unable to produce sputum.
CoP and CoR= correlate of protection and correlate of risk
Note that all blood samples collected on Days 1 and 29 will be collected prior to study intervention administration.
Laboratory test results of samples collected at screening visit will be utilized to determine eligibility.
Laboratory test results of blood samples collected on Day 1 will be used to establish baseline pre-vaccination values (and not to determine eligibility), and blood samples collected at Day 29 will be used to establish baseline

values prior to the administration of the second dose (and not to determine eligibility for second dose administration).
Added space between sentences: All blood volumes are approximate. Total amount of whole blood...

Note that ***the*** sponsor will evaluate whether alternative methods for safety assessments…

Section 2.1 Background TB-014: ~~y~~***Y***ear 3

Section 5.2: Exclusion Criteria: capitalized the word Assessment: Diagnostic ***A***~~a~~ssessments

Added new number 9. ***Receipt of any vaccine in the period starting 7 days before, and ending 7 days after, each dose of the study vaccine. Refer to Section 6.4***

Renumbered criteria starting with **Prior/Concurrent Clinical Study Experience,** changed 9 to 10, 10 to 11, etc.

Added new number 15 under diagnostic assessments: ***Indeterminate QFT result***

Renumbered criteria under "Other Exclusions to 16 – 20 (previously 14 – 18).

New 17. Corrected typographical error: deleted extra "," in TB,~~,~~e.g.,

New 18. Female participant……study ~~product~~ ***intervention*** (for consistency)

New 20. Corrected spelling error *Defined as provided that the arrangements falls~~~~ within the…

Section 5.3 Screen Failures

- When there are technical difficulties with phlebotomy at screening (e.g., laboratory report***s*** hemolyzed blood~~).~~***), technical error in running the laboratory tests, or an abnormal urine analysis (e.g., due to menstruation or urinary tract infection).***

Section 6.1.1 Administration

Before administering the injection, the study intervention administrator must ~~inspect the syringe and vaccine volume,~~ check~~ing~~ that the syringe is identified with the correct participant identification number and check~~ing~~ the date and time the dose was prepared.

Section 6.1.2 Preparation/Handling/Storage/Accountability

Further guidance and information for the preparation, handling, storage and accountability are provided in the Study ~~Reference~~***Pharmacy*** Manual.

Section 6.1.3 Vaccine Administration Error

Each vaccine dose will be prepared by reconstituting fully the contents of one vial containing the antigen with the contents of one vial of the adjuvant, and then drawing out the reconstituted vaccine content ***(0.5 mL)*** ~~fully~~ into the dosing syringe.

Section 6.2.2 Masking

All unblinded persons must take care to not reveal individual group assignments to any other member of the study team. ***The investigational pharmacist preparing study interventions will be unblinded but will not perform other study duties***. ~~Designated unblinded site staff will prepare the vaccine in a blinded manner (the kits and doses are provided in a blinded manner).~~

A delegation of authority log will be maintained by the site and will identify the individual(s) ~~authorized to function as the study vaccine manager, i.e., individuals~~ with access to study blinding information.

Section 6.4 Concomitant Therapy

* The use of anti-inflammatory and antipyretic medication should be discouraged during the first 28 study days (~~D~~***d***ays 1 through 28~~)~~ after each dose administered***)***.

Added: ***Receipt of any vaccine 7 days before and 7 days after either Dose 1 or Dose 2 is prohibited during the study, and will lead to study withdrawal. Refer to Section 7.2.***

Section 7.2 changed title of section: Participant ~~Discontinuation~~/Withdrawal from the Study (changed because discontinuation not mentioned in this subsection).

If the participant withdraws consent ~~for disclosure of future information,~~ the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Added new bullet after pregnancy bullet: ***Receipt of any vaccine 7 days before and 7 days after Dose 1 and after Dose 2***

Section 7.3 Title: Lost to Follow**-**up; added hyphen in follow-up

Section 8. Study Assessments and Procedures

In addition, safety laboratory tests (hematology ***and*** chemistry), and urinalysis~~)~~ ***(including microscopy)*** as well as a QFT TB test, sputum Xpert MTB/RIF assay, $CD4^+$ cell count, HIV viral load, HIV serology, hepatitis B and C screening, and a serum pregnancy test (females only)

All protocol-required safety laboratory tests (hematology, chemistry, and urinalysis) as well as a QFT TB test, sputum Xpert MTB/RIF assay, CD4+ cell count, HIV viral load, HIV serology, hepatitis B and C screening, and a serum pregnancy test (females only) will be performed by the central laboratory, Bio Analytical Research Corporation RSA (BARC SA or similar).

Urine pregnancy tests will be performed by the study site.

Assays for secondary and exploratory endpoints will be carried out in laboratories outside of the RSA.

Section 8.1.1. Humoral Immunogenicity added text:

*…**(Table 2). On Day 1 and Day 29 visits, samples will be collected prior to study intervention administration.***

Section 8.1.2. Cell-Mediated Immune Responses

On Day 1 and Day 29 visits, samples will be collected prior to study intervention administration.

For the secondary objective, frequency and magnitude of M72-specific CD4+ and CD8+ T-cell responses will be measured by expression of IFN-γ or IL-2 at Days 1, 57 and 390 to

characterize the vaccine-induced immune response at baseline, peak immunogenicity and long-term memory, respectively.

If responses at peak or memory are lower than expected compared to historical data from previous M72 vaccine studies, additional timepoints may be assessed to further characterize the kinetics of the cellular vaccine-induced immune response in HIV-positive study participants.

For exploratory objectives, polyfunctionality of M72-specific CD4+ and CD8+ T-cell responses will be measured to support the exploratory objective by analysis of the co-expression of multiple functional markers by ICS.

Section 8.2.1. Physical Examination and Medical History

As part of ~~screening,~~ ***the history/physical examination at each visit,*** a TB symptom/sign checklist ***from RSA TB guidelines*** will be used. This will include TB contact history. ~~If TB is suspected, potential participants would be managed according to standard of care~~. ***The TB symptom/sign checklist in the eCRF includes:***

- ***Cough for longer than 2 weeks***
- ***Fever for longer than 2 weeks***
- ***Fatigue for longer than 2 weeks***
- ***Night sweats for longer than 2 weeks***
- ***Loss of weight or insufficient weight gain or growth***
- ***Other.***

If TB is suspected, potential participants would be managed according to standard of care.

Section 8.2.4. Diary Card and Daily Temperature Monitoring

The diary card will be collected and reviewed by the PI (or designee) ~~on~~ 7 days after each dose, ***i.e.***~~ie~~, on Day 8 (Visit 2) and Day 36 (Visit 4). No changes to the diary card will be permitted,

Section 8.2.5. Clinical Safety Laboratory Assessments

- Urinalysis ***by dipstick***: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase~~, by dipstick~~
- ***Urine microscopy.***

Section 8.2.8. Sputum Xpert MTB/RIF

A single self-expectorated sputum will be collected for Xpert MTB/RIF assay ~~**at screening**~~ ***from all participants at screening, and from participants with suspected TB, at study visits.*** Participants with a positive sputum Xpert MTB/RIF assay ***at screening*** (if sputum is able to be collected) are ineligible for the study***.*** ~~and.~~ ***All participants with a positive sputum Xpert MTB/RIF assay and/or suspected TB*** should be referred for further management per standard of care.

Section 8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the participant (or, as appropriate, the participant's legally authorized representative). Biochemistry and/or hematology findings may also qualify as AEs if the investigator considers them as such.

~~All SAEs and AESIs, will be collected through the end of the study.~~

Refer to Table 5 for the required time periods for collection of each type of AE.

Section 8.3.1 added "and Pregnancy" to title**: Time Period and Frequency for Collecting AE, ~~and~~ SAE, *and Pregnancy* Information**

Added table number and title: Table 5 Collection Period for all AEs and Pregnancies

Type of Event	Collection Time Period
Any AE, SAE, or AESI	***From time of ICF and/or IAF is signed until dosing at Day 1***
All solicited AEs	***7 days after each dose*** ~~Day 1 through Day 7 (inclusive) after each dose~~
Unsolicited AEs	***28 days after each dose*** ~~Day 1 through Day 28 (inclusive) after each dose~~
All SAEs, AESIs ***and Pregnancies***	Day 1 through Month 13 (Day 390) (end of study)

~~Medical conditions that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.~~

Section 8.3.3.1 AE Intensity

Unsolicited AEs will be**…..**

Solicited AEs will be graded by the participant using the diary card.

Section 8.3.3.2. AE Causality

The sponsor or designee will never downgrade a case from serious to non-serious~~, or related to not related~~.

Section 8.7 Exploratory Biomarkers

If future research must be conducted in countries other than RSA**,** a separate ***request for approval will be made to the IRB/IEC***, informed consent/assent will be required, and is subject to laws and regulations of the RSA and to IRB/IEC approval.

Numbering of table changes:

Section 9.2, Table 5 changed to Table 6.
Section 9.3, Table 6 changed to Table 7.
Section 9.4, Table 7 changed to Table 8.

Section 9.3 Table 7

Population	Description
Randomized	***All participants randomly assigned to study intervention, a randomization number and date.***
Modified intention to treat (mITT) population.	All participants randomly assigned to study intervention and who received the study intervention ***and who were randomly selected and tested for immunogenicity***. Participants will be analyzed according to the intervention they actually received.
Per-Protocol for Immunogenicity Population	***All participants in PP population randomly selected to have immunogenicity assays performed.***

Section 9.4 Statistical Analyses, Table 8: Summary of Endpoints and Analyses

Secondary Endpoints	Statistical Analysis
M72-specific antibody titer ~~pre- and post-vaccination through the end of the study~~ ***at Day 1, Day 29, Day 57, Day 210 and Day 390***	Anti-M72/AS01$_E$ seropositive rates and GMCs will be calculated by treatment and time point with exact 95% CIs.
Frequency, ***and*** magnitude ~~**and polyfunctionality**~~ of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured **by** ***expression of IFN-γ or IL-2*** by ICS ~~**pre- and post-vaccination through the end of the study**~~ ***at Day 1, Day 57 and Day 390***	The frequency of CD4$^+$ T cells positive for IFN-γ or IL-2, by ICS, will be summarized by treatment group and timepoint. Median DMSO-subtracted cytokine responses and associated 95% CIs will be used to summarize percentage T cell responses.
Exploratory Endpoints	**Statistical Analysis**
Frequency and magnitude of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by expression of IFN-γ or IL-2 by ICS at Day 29 and Day 210	***The frequency of CD4$^+$ T cells positive for IFN-γ or IL-2, by ICS, will be summarized by treatment group and timepoint. Median DMSO-subtracted cytokine responses and associated 95% CIs will be used to summarize percentage T cell responses.***
Polyfunctionality of M72-specific CD4$^+$ and CD8$^+$ T-cell responses measured by co-expression of multiple functional markers by ICS	***Polyfunctionality will be analyzed by COMPASS*, and summarized by treatment group using functionality and/or polyfunctionality scores.***
Suspected TB during the study	***Summary statistics will be generated for the incidence of suspected TB by treatment group and timepoint.***

Laboratory-confirmed pulmonary TB during the study	***Summary statistics will be generated for the incidence of Laboratory-confirmed pulmonary TB by treatment group and timepoint.***

* [Lin 2015]

Section 9.4.3. Exploratory analyses

Summary statistics will be generated for the incidence, by treatment group, of suspected TB disease and laboratory-confirmed pulmonary TB that occur throughout the study period.

Section 9.5.2.1 Informed Consent forms

~~Laboratory assays for primary and secondary endpoints will be carried out in the RSA.~~

Participants will also be informed that laboratory tests will be run in laboratories in and outside of the RSA.

Section 9.6.5 Recording and Follow-Up of AE and/or SAE

Study product changed to study intervention

Section 9.7 Contraceptive Guidance and Collection of Pregnancy Information
Contraception Guidance:

Added "after the start of": Women physically capable of pregnancy must agree to use an acceptable method of avoiding pregnancy **for one year *after the start of*** **study intervention**.

Collection and Reporting Pregnancy Information

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded ~~on the appropriate form~~ and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

Section 9.8 Toxicity Table:

page 74: added the subscript 1 before the note: [1] Blood pressure norms for children < 18 …

page 78: added the subscript 1 before the note: [1] Definition: A disorder characterized by …

page 83: added rows for osteopenia and for osteoporosis ≥ 30 years of age

≥ 30 years of age	***BMD t-score-2.5 to -1***	***NA***	***NA***	***NA***
≥ 30 years of age	***NA***	***BMD t-score < -2.5***	***Pathologic fracture (e.g., compression fracture causing loss of vertebral height)***	***Pathologic fracture causing life-threatening consequences***

page 97: added the subscript 1 before the note: [1] Injection Site Erythema or Redness should be …

page 101: added the subscript 1 before the note: [1] Creatinine clearance- Use the applicable…

Section 10 References

Added: ***Lin L, Finak G, Ushey K, et al. COMPASS identifies T-cell subsets correlated with clinical outcomes. Nat Biotechnol. 2015 Jun;33(6):610-6. doi: 10.1038/nbt.3187. Epub 2015 May 25.***

Signature Page for TBV02-202 Protocol Version 3.0 v4.0

Approval	[redacted]ment 26-Feb-2021 20:30:40 GMT+0000

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