STATISTICAL ANALYSIS PLAN

Protocol HPTN 077

A Phase IIa Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, GSK1265744, in HIV-uninfected Men and Women

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Version 2.2

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SAP Modification History

SAP modified SAP v1 according to the protocol HPTN 077 final version 3.0 that includes the second cohort.

SAP v2.1 modified SAP v2 according to Letter of Amendment #3 to HPTN 077.

SAP v2.2 updated tables and figures templates for the final study report and added an algorithm of defining the phase for AEs

Table of Contents

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides details on planned study statistical analyses and reports for HPTN 077. This SAP is required prior to the first analysis and must be approved by the protocol chair and reviewed by GSK statistician. The plan might be updated if needed prior to any interim analyses and before the final analysis. Any updates will be archived. The contents of SAP are based on the protocol HPTN 077 final version 3.0 and are modified to extend the tail visits according to Letter of Amendment #3.

2 PROTOCOL SUMMARY

2.1 Title

A Phase IIa Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, GSK1265744, in HIV-uninfected Men and Women

2.2 Primary Objectives

- Evaluate the safety and tolerability of the injectable agent GSK1265744 long acting (744LA) injectable (800 mg dose administered at three time points at 12 week intervals), through Week 41 in HIV-uninfected men and women.
- Evaluate the safety and tolerability of the injectable agent GSK1265744 long acting (744LA) injectable (600 mg dose administered at two time points at 4 week intervals, followed by three time points at 8 week intervals), through Week 41 in HIV-uninfected men and women.

2.3 Study Product Regimens/Administration/Formulation Content

Study Product Regimens

Both Cohorts:

Oral lead-in phase: Participants will be randomized 3:1 to one of two study arms:

- Arm 1: GSK1265744 tablets 30 mg – one tablet orally daily for 4 weeks, with or without food
- Arm 2: Placebo for GSK1265744 – one tablet orally daily for 4 weeks, with or without food

Injectable phase: After a one week washout period to assess safety, participants will begin injections (with the same randomization as the oral lead-in phase) as:

Cohort 1:

- Arm 1: GSK1265744 (744 LA) 800 mg administered as two 2 mL (400 mg) IM injections in the gluteal muscle at Weeks 5, 17, and 29

- Arm 2: Placebo for GSK1265744 (744 LA Placebo) administered as two 2 mL injections in the gluteal muscle at Weeks 5, 17, and 29

Cohort 2:

- Arm 1: GSK1265744 (744 LA) 600 mg administered as one 3mL (600 mg) IM injections in the gluteal muscle at Weeks 5, 9, 17, 25 and 33

- Arm 2: Placebo for GSK1265744 (744 LA Placebo) administered as one 3 mL injections in the gluteal muscle at Weeks 5, 9, 17, 25 and 33

Study Product Formulations

Oral product:

- GSK1265744 tablets 30 mg are formulated as white to almost white oval-shaped coated tablets for oral administration. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closure that include an induction seal. The bottles contain a desiccant. The bottles should be stored up to 25 degrees Celsius (25^{o} C) and protected from moisture.
- Placebo tablets for GSK1265744 are formulated as white to almost white oval-shaped coated tablets to visually match the active GSK1265744 tablets. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closure that include an induction seal. The bottles contain a desiccant. The bottles should be stored up to 25 degrees Celsius (25^{o} C) and protected from moisture.

Injectable Suspension:

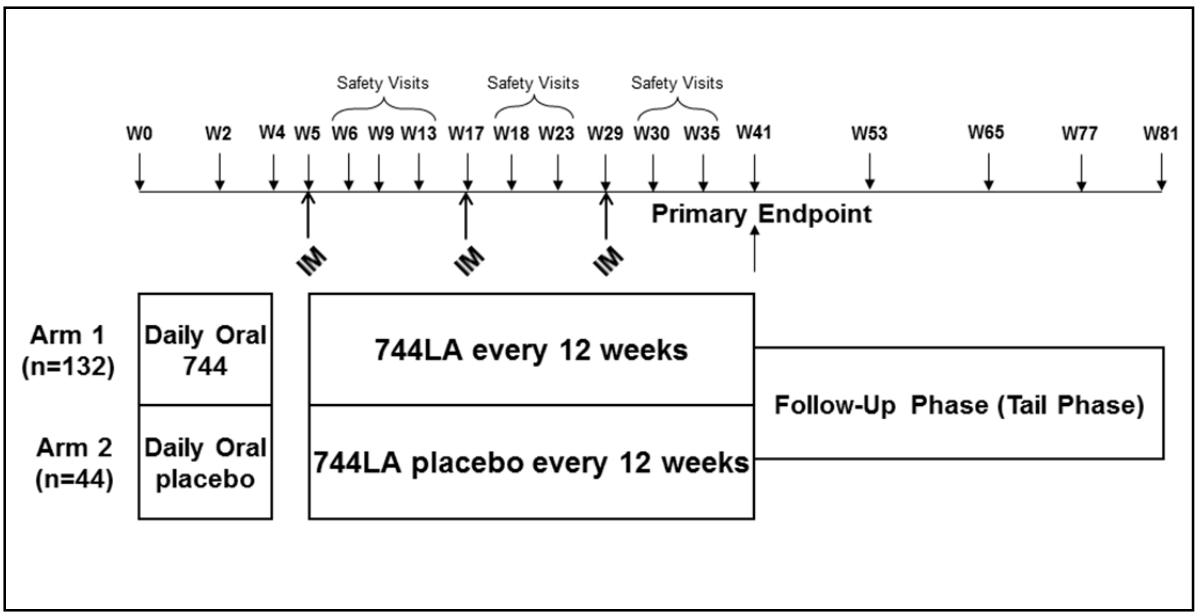
- The GSK1265744LA is formulated as a sterile white to slightly colored suspension containing 400mg/2mL of GSK1265744 for administration by intramuscular (IM). Th e product is packaged in a 3 mL vials. Each vial is for single use containing a nominal fill of 2mL (400 mg), and does not require dilution prior to administration. The GSK1265744LA injectable suspension is to be stored at 2 degrees Celsius to 30 degrees Celsius (2^{o} C – 30^{o} C), do not freeze.
- Placebo for GSK1265744 Injectable Suspension will be Sodium Chloride for Injection USP, 0.9%.

Syringes containing active and placebo study product will be covered with an overlay by the study Pharmacist of Record or designee prior to dispensing in order to maintain the blind, as per the SSP Manual.

The study product being tested in this study is investigational and not yet approved by the US FDA for the treatment or prevention of HIV-1 infection. Further information on the study product is available in the Investigator's Brochure, which will be provided by the DAIDS Regulatory Support Contract (RSC).

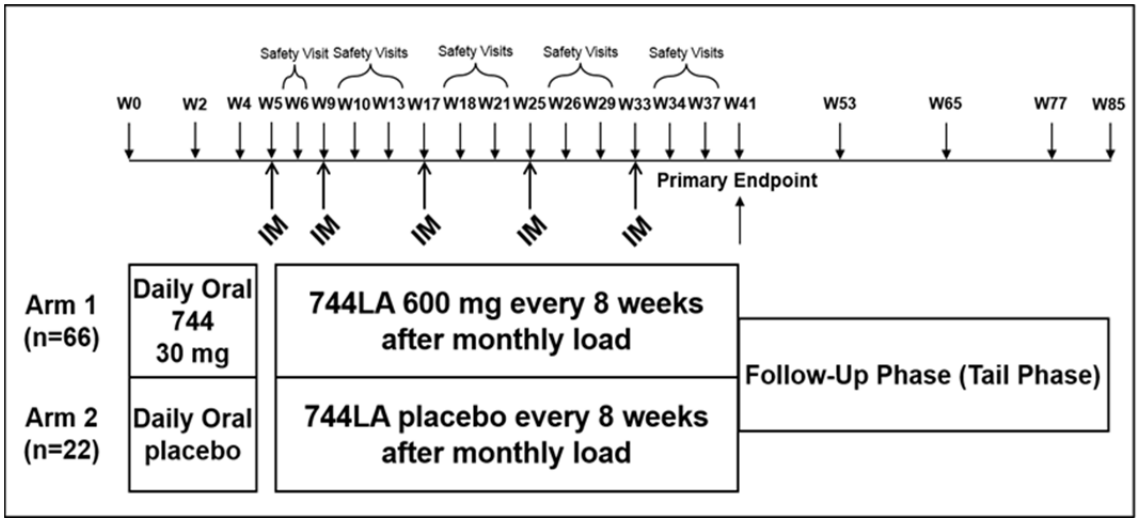
2.4 Schema

Cohort 1



W = Week

Cohort 2



The 110 participants in Cohort 1 and 90 participants in Cohort 2 were randomized to one of the two study arms with an active GSK 744 to placebo ratio of 3:1, stratified by gender and region (US and non US), as follows:

Cohort 1

Arm 1: 82 participants received daily oral 744 (30 mg tablets) for 4 weeks, followed by an one week washout period, to establish safety and tolerability, followed by intra-muscular (IM) gluteal injections of 800 mg of 744LA (administered as two sequential 400 mg gluteal injections) at three time points at 12 week intervals as: Week 5, Week 17, and Week 29.

Arm 2: 28 participants received daily oral matching placebo and IM injections of vehicle-matched placebo on the same schedule as Arm 1.

Cohort 2

Arm 1: Approximately 66 participants will receive daily oral 744 (30 mg tablets) for 4 weeks, followed by a one week washout period, to establish safety and tolerability, followed by intra-muscular (IM) gluteal injections of 600 mg of 744LA (administered as one 600 mg gluteal injection) at five time points at 4 and 8 week intervals as: Week 5, Week 9, Week 17, Week 25, and Week 33.

Arm 2: Approximately 22 participants will receive daily oral matching placebo and IM injections of vehicle-matched placebo on the same schedule as Arm 1.

All participants will receive HIV testing with pre- and post-test counseling, in addition to risk-reduction counseling and condoms and lubricant. All participants will be followed according to the Schedule of Evaluations and Procedures provided in HPTN077 protocol Appendices I-IV.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

Primary Objective

- Evaluate the safety and tolerability of the injectable agent, GSK1265744 long acting (744LA) injectable (800 mg dose administered at three time points at 12 week intervals) through Week 41 in HIV-uninfected men and women
- Evaluate the safety and tolerability of the injectable agent GSK1265744 long acting (744LA) injectable (600 mg dose administered at two time points at 4 week intervals, followed by three time points at 8 week intervals), through Week 41 in HIV-uninfected men and women.

Primary Endpoints

Safety endpoint: Proportion of participants experiencing any Grade 2 or higher clinical AEs and laboratory abnormalities that occur from the initial injection to 12 weeks after the last injection among participants who receive at least one injection (injectable phase only)

Tolerability endpoint: Proportion of participants who receive at least 1 injection and who discontinue receiving injections prior to the full course of 3 injections due to intolerability of injection (including but not limited to ISR), frequency of injections, burden of study procedures, or any AE.

These cohorts may be aggregated for an overall analysis if appropriate.

3.2 Secondary Objectives and Endpoints

Secondary Objectives

- Evaluate the safety and tolerability of GSK1265744 (daily oral 744 + 744LA) for 76 weeks of follow-up after final injection (each cohort will be analyzed separately)
- Evaluate the safety and tolerability of oral 744 from Week 0 to Week 5

- Evaluate the pharmacokinetics of 744LA administered as 800 mg IM every 12 weeks for 52 weeks of follow-up after final injection
- Evaluate differential pharmacokinetics of 744LA in participants by age, gender, race, ethnicity, weight, body mass index (BMI), and smoking status
- Evaluate the acceptability of 744LA injections
- Evaluate the effect of 744LA on sexual risk behavior by change from enrollment for repeat assessments to during the study period
- Evaluate HIV incidence and antiretroviral drug resistance, if any participants acquire HIV infection during the study
- Evaluate the safety, tolerability and pharmacokinetics of 744LA in the subset of women who use a hormone-based contraceptive

Secondary Endpoints

- Proportion of participants who discontinue either oral or injectable study product for reasons of toxicity, tolerability, or acceptability prior to completion of the full oral and injectable phases
- Proportion of participants experiencing Grade 2 or higher clinical AEs and laboratory abnormalities during 52 weeks following final injection (safety) and any AE that leads to discontinuation (tolerability) during the aggregate oral and injectable phases
- Proportion of participants experiencing Grade 2 or higher clinical AEs and laboratory abnormalities (safety) and any AE that leads to discontinuation (tolerability) in the oral phase and washout period
- Plasma drug levels of GSK1265744 at designated time points after each injection of 744LA (by cohort only)
- Plasma drug levels of GSK1265744 at designated time points after each injection of 744LA stratified by age, gender, race, ethnicity, weight, BMI, and smoking status
- Proportion of participants willing to use an injectable agent such as the study product for HIV prevention in the future
- Change from enrolment of self-reported sexual behaviour (number of sexual partners, episodes of unprotected anal and/or vaginal intercourse) during the study period using a standardized assessment tool (in aggregate only)
- Number of incident HIV infections through the study period, including number with treatment emergent resistance
- Proportion of injectable hormonal-contraception-using female participants who reach a safety or tolerability endpoint as defined above

3.3 Exploratory Objectives and Endpoints

Exploratory Objectives

- Explore relationships between safety parameters and GSK1265744 concentrations and/or participant demographic factors
- Explore genetic factors that may impact the pharmacokinetics of 744LA
- Perform secondary laboratory assessments which may include evaluation of factors related to HIV infection, hepatitis infection, or sexually transmitted infections (STIs); antiretroviral (ARV) drug use; pharmacogenomics; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives

Exploratory Endpoints

- Relationships between observed AEs and pharmacokinetic parameters (including but not limited to GSK1265744 C_{max} and C_{min} and AUC) and participant demographic data (individual and in aggregate)
- Relationships between pharmacogenetics (evaluated by Genome Wide Association Study [GWAS], which will inform subsequent targeted analyses) and pharmacokinetic parameters or incidence of AEs (any and by organ class and individual AE)

4 STUDY DESIGN

4.1 Participants

200 men and women at low to minimal risk for acquiring HIV infection, ages 18 to 65, randomized 3:1, with approximately 150 in the active drug arm, and 50 in the placebo arm. It is anticipated that approximately 60% of the enrolled participants will be women.

4.2 Design

This is a multi-site, double-blind, two-arm, randomized, placebo-controlled trial of the safety, tolerability, and acceptability of 744LA.

4.3 Study Duration

Approximately 3 years. Accrual will require approximately 16 to 24 weeks (4 – 6 months) for each cohort. Study participants in both cohorts will receive oral tablets for 4 weeks, followed by a 1 week wash out period. Cohort 1 will then receive intra-muscular injections at 3 time points over 24 weeks (6 months); cohort 2 will receive intra-muscular injections at five time points over 28 weeks (7 months). Participants in the active study product arm will be followed for 76 weeks (18 months) after their last injection. Participants in the placebo arm will be followed until 76 weeks after their last injection or until the last participant in the active study product arm in cohort 2 completes their Week 41 visit, whichever comes first, at which time the study will be unblinded to assess the primary endpoint. When all procedures related to unblinding are completed, participants in the placebo arm will no longer be followed.

4.4 Study Visits

Cohort 1:

- Week 0: enrollment visit
- Weeks 2 and 4: oral phase safety visits
- Week 5: the first injection visit
- Weeks 6, 9, 13: safety visits after the 1st injection
- Week 17: the second injection visit
- Weeks 18 and 23: safety visits after the 2nd injection
- Week 29: the third injection
- Weeks 30, and 35: safety visits after the 3rd injection
- Week 41: primary endpoint visit
- Weeks 53, 65, 77, 89, 101: tail phase safety visit
- Week 105: final study visit.

Cohort 2:

- Week 0: enrollment visit
- Weeks 2 and 4: oral phase safety visits
- Week 5: the first injection visit
- Week 6: safety visits after the 1st injection
- Week 9: the second injection visit
- Weeks 10 and 13: safety visits after the 2nd injection
- Week 17: the third injection visit
- Weeks 18 and 21: safety visits after the 3nd injection
- Week 25: the forth injection
- Weeks 26, and 29: safety visits after the 4th injection
- Week 33: the fifth injection visit
- Week 34 and 37: safety visits after the 5th injection
- Week 41: primary endpoint visit
- Weeks 53, 65, 77, 89, 101: tail phase safety visit
- Week 109: final study visit.

4.5 Allowable Visit Windows

The allowable visit windows for all visits, including injection visits, are outlined in Section 12 Data Management of SSP Manual. The allowable visit windows are pre-specified around the targeted visit windows. If a participant is unable to report to the visit during this time frame, or if a participant misses his/her appointment within the visit time frame, the CMC must be contacted for consultation regarding whether rescheduling outside of the visit window is allowable. Visits that occur outside of the allowable visit windows are coded either late or early.

4.6 Study Sites

HIV Prevention Trials Network (HPTN)-affiliated Clinical Trial Units (CTUs) and/or Clinical Research Sites (CRSs) participating in this study is listed in the SSP Manual, and include sites in Brazil, sub-Saharan Africa (SSA), and the United States (US).

4.7 Randomization

Enrolled participants are randomized to one of two study arms with an active GSK1265744 to placebo ratio of 3:1 in two cohorts. The arm randomization is stratified by

gender and region (US and non-US sites) and done in blocks to ensure balanced treatment assignments within each gender and region (US and non-US). The randomization scheme is generated, operationalized and maintained by HPTN SDMC using Frontier Science & Technology Research Foundation, Inc. (FSTRF) system. Additional details regarding the process of randomization are included in the SSP Manual.

4.8 Blinding

Study site staff, with the exception of the site Pharmacist of Record or their designee, and participants will be blinded to the random assignments. Blinding will be maintained until the last participant enrolled in to the active drug arm in cohort 2 has completed their Week 41 visit (the time point of the primary endpoint of the study), and when all data related to the Week 41 visit has been entered into the database, as well as cleaned and verified. At a specified time directed by the HPTN SDMC, participants will be unblinded to their treatment assignment, and participants in the placebo arm will no longer need to be followed. Participants in the active study product arm will continued to be followed for 52 weeks after their last injection.

5 PLANNED ANALYSES

5.1 SMC Report

The HPTN Study Monitoring Committee (SMC) will be utilized in this study to ensure objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study. The SMC will conduct interim reviews of the study data approximately every 6 months. Study data including rates of subject accrual, visit retention, progression of primary and main secondary endpoint assessments, data collection and laboratory issues will be shared by the study team with the SMC in an open session. In a closed report, safety data by unblinded treatment arm will be provided to the SMC by HPTN SDMC in the closed report.

The first SMC review will be conducted when approximately 50% of the subjects complete Week 17 (second injection) and at least every six months thereafter.

5.2 Interim Analysis

An interim analysis will be performed when 50% of the participants have completed their primary endpoint visit (Week 41). All data available at that time will be included in the analysis. Pharmacokinetic data will be analyzed when approximately 50% of Cohort 1 reaches Week 29 (two troughs) for Cohort 1 participants, and when approximately 50% of Cohort 2 reaches Week 17 (two troughs) for Cohort 2.

With the approval from HPTN SMC, the unblinded summaries of the safety and pharmacokinetic data from the analysis may also be provided to the key members of the protocol team and possibly to regulatory agencies to facilitate an initiation of a phase III trial. All members of the protocol team, including GSK and ViiV Healthcare, as well as study participants will remain blinded to individual participant treatment assignment. The data from this analysis may also be combined with the interim data from a similar study being conducted by GSK/ViiV, if needed and appropriate. Pooled summaries will also be provided to the study team to share with regulators.

To maintain the integrity of the clinical study, only the following staff may be unblinded at these SMC interim analyses, as deemed necessary by the SMC: selected clinical

pharmacometrician, programmer, and statisticians who will use unblinded 744 concentrations to build the population PK models, and staff who will incorporate safety data from this analysis into regulatory documents for other studies of 744. The primary study team (medical monitor, clinical study team leader, operational scientist, data manager) should remain blinded until all subjects complete the week 41 visit and the data has been entered and cleaned and all major protocol violators have been identified. The primary study team will only receive unblinded summary tables and figures for the planned interim analysis.

5.3 Primary Analysis

A clinical database will be authorized and released for reporting on the unblinded 41-week safety and tolerability results that encompass the primary endpoints of this study. These findings will be used for internal decision making, possible reporting at scientific meetings, and as needed for regulatory submissions.

5.4 Final Analysis

The final planned analyses will be performed after all participants have completed the follow-up phase and after database freeze.

6 STUDY POPULATIONS

The data collected from the enrolled participants will be analyzed according to the actual treatment that the participants have received. A subset of the enrolled participants might be evaluated in some analyses. For instance, in the primary safety analysis, the safety data from the participants who have completed at least one injection will be analyzed. We define this subset of the enrolled participants as the Injectable/Primary Safety Population below in Section 6.4.

6.1 Screened Population

The Screened Population will consist of all participants who are screened for inclusion in the study.

6.2 Randomized Population

The Randomized Population will consist of all participants who meet the study criteria and are randomly assigned to a treatment in the study at the enrollment date.

6.3 Safety Population

The Safety Population will consist of the participants who are enrolled in the study and have received at least one dose of the study product. In the analyses, the participants will be grouped based on the initial randomization assignments regardless how many doses of the study product they have received.

6.4 Primary/Injectable Safety Population

The Primary/Injectable Safety Population is a subset of the Safety Population that consists of the participants who have received at least one injection of study product. In the analyses, the participants will be grouped based on the initial randomization assignment regardless how many injections they have received.

6.5 Pharmacokinetic Concentration Population

The Pharmacokinetic Concentration Population will consist of the participants in the Injectable Safety Population who have plasma sample(s) collected for PK assay.

6.6 Pharmacokinetic Parameter Population

The Pharmacokinetic Parameter Population will consist of the participants in the Injectable Population who are also assigned to receive the 744 study product and have available samples for PK assay.

6.7 Pharmacogenomic Population

The Pharmacogenomic Population will be determined later.

7 ASSESSMENT WINDOWS

7.1 Treatment Periods

Adverse events, laboratory, vital signs and liver events will be assessed and denoted within the treatment periods that are defined below.

Oral Phase is defined as the time between the enrollment date (Week 0) and the day of the 1st injection (Week 5) or the day of withdrawal, whichever comes first.

Injection Phase is defined as the time between the first injection and the 12 weeks visit after the last injection. For the participants who complete all three injections, the injection phase assessment window is the time between Week 5 and Week 41 visits. For the participants who complete the two injections, the injection phase assessment window is the time between Week 5 visit and Week 29 visit. For the participants who complete only the first injection, the injection phase assessment window is the time between Week 5 visit and Week 17 visit.

Tail Phase is defined as the time between Week 41 to Week 105/109 for ITT analysis. However, for per protocol analysis such as pharmacokinetics analysis, for the participants who did not complete full injections (3 injections for cohort 1 and 5 injections for cohort 2), the tail phase assessment window starts at the 12th (the 8th) weeks after the last injection for cohort 1 (cohort 2) to the last follow-up visit.

On-Treatment is defined as the time between the beginning of the oral phase and the end of the follow-up phase (from the participants' enrollment day to the participants' last day subject's last day in the study).

7.2 Baseline Definition

The data collected at the enrolment date will be considered as the baseline data for minoring and evaluating the safety, tolerability, and acceptability of the investigating study product and other analyses unless it is specified. In some cases, the assessments at Week 5 prior to the first injection will be considered as the baseline.

8 DATA HANDLING/MANAGEMENT

All data will be collected and saved in CRF database and laboratory database. The details of data collection and data management are provided in Section 12 Data Management in SSP.

8.1 Premature Withdrawal and Missing Data

8.1.1 Premature Withdrawal

The reason(s) for withdrawal from the study must be recorded by the investigator in the CRF, including the participant's reason for withdrawn consent. Withdrawn participants will not be replaced. All available data from those who withdraw from the study earlier will be included in the analyses according to the study populations defined in Section 6. In the case that the study is prematurely discontinued, all available data will be used in the analyses that are still considered appropriate.

8.1.2 Methods for Missing Data

Missing data will occur when any requested data is not provided, leading to blank fields on the collection instrument. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. Missing data will occur if the participants will miss visits and withdraw from the study prior to complete the study regimen.

8.2 Derived and Transformed Data

8.2.1 Age

The participants' date of birth or age will be recorded in CRF. If the age is not recorded in CRF, the age will be calculated based on the date of birth and the date of the completion of the CRF. In a case that the date of birth will be used in the calculation of the age, if the date of birth is partial missing, the missing month will be imputed by June; the missing day

will be imputed as the 30th; Otherwise, if the date of birth is missing completely, the date of birth will not be imputed and the age will be missing.

8.2.2 Changes from the Baseline

For the variables that the changes from the baseline will be evaluated in the analyses, the changes will be calculated by subtracting the baselines values of the variables from the values at post-baseline visits. If the baseline or the post-baseline value is missing, then the change from the baseline will be missing.

8.2.3 Corrected QT Intervals

The corrected QT interval measured by Bazett's (QTcB) or Fridericia's (QTcF) will be recorded in CRF.

9 STATISTICAL DATA ANALYSES

All data from enrolled participants will be analyzed according to the Analysis Populations described in Section 6.

9.1 Analysis Tools

Analyses for primary endpoints will be performed in SAS. All other descriptive and inferential statistical analyses will be performed using SAS and/or R statistical software.

9.2 Analysis Variables

The analysis variables consist of baseline participant characteristics, safety, tolerability, acceptability, sexual risk behavioral, and pharmacokinetics for primary, secondary, and exploratory analyses.

9.3 General Approach

When the use of descriptive statistics to summarize the study populations' characteristics is required, the following statistics will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). When the use of a statistical test to assess the difference between two different time points within each the treatment arm is required, the following tests will be used: for categorical variables, McNemar test; for continuous variables the paired t-test or Wilcoxon signed-ranks test. When use of a statistical test to assess the differences between the two treatment arms is required, the following tests/models will be used: for binomial response variables, chi-square tests (Fisher Exact test will be used if there are cells with less than 5) or logistic regression models if other covariates need to be adjusted in the model; for continuous variables, t-test if the data are normal distributions) or nonparametric Wilcox rank sum test if data are not normally

distributed or linear regression models if other covariates need to be adjusted. Additional analyses will also be performed and described below.

To assess the adequacy of the randomization, participants in each of the two arms will be compared for baseline characteristics including demographics and laboratory measurements.

9.4 Baseline Characteristics

A table that includes the baseline characteristic variables of the enrolled participants will be presented. Summary statistics appropriate for the measurement scale will be used to describe the distribution of these variables. These summary statistics will be presented in tables by cohort and study arm among the enrolled participants in the oral phase and as well as among the participants that will be enrolled in the injection phase. Baseline characteristics will be compared between two study arms using chi-square test for categorical variables such as gender and using t-test or for continuous variables. The summary tables will be also stratified by US sites and Non-US sites to see whether theses baseline measures differ by US sites vs international sites. The comparisons between the two treatment arms will be adjusted for sites (US vs. Non-US) if the differences are observed between US and Non-US sites.

9.5 Safety Analysis

Safety data will be analyzed using the data from the safety populations described above respectively for each safety analysis. Safety will be analyzed by cohort and in aggregate.

9.5.1 Injection Site Reaction (ISR)

The number and percentage of participants experiencing each type of ISR sign or symptom will be tabulated by severity and treatment arm. For a given sign or symptom, each participant's ISR will be counted once under the maximum severity for all injection visits as well as by each successive injection. ISR other characteristics will be summarized by treatment arm and injection.

If a participant is observed with any inflammation symptom, the participant's temperature will be taken and reported in ISR CRF. The temperature will be graded according to the DAIDS Grading Table 2014 V2.0 and will tabulated by study arm by each injection and compared between the two arms using Chi-square test.

9.5.2 AEs

AEs will be summarized using MedDRA system organ class and preferred terms. The number and percentage of participants experiencing each specific AE within a System Organ Class or within preferred term will be tabulated by severity or by relationship to study product within each treatment arm. For the calculations in these tables, a participant with multiple AEs within a category during the evaluating phase of the study will be counted once under the maximum severity or the strongest recorded causal relationship to study product. AEs will be summarized for those that will occur during the injection phase separately from those that will occur during the oral phase and as well as for those that will occur during the entire treatment phase of the study (the oral and the

injection phase). AEs leading to temporarily or permanently stopping drug will also be summarized by treatment arm.

A listing of EAEs reported to the DAIDS RSC Safety Office will provide details of the events including severity, relationship to study product, time between onset and last injection, number of injections received, and a summary of the event.

9.5.3 Local Laboratory Values

Scatter plots of some local laboratory values measured during the course of the study vs. the values at the baseline. If appropriate, horizontal/vertical lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will also be presented by treatment arm and visit time, as well as changes from baseline for post-enrollment values. Clinical laboratory abnormalities without an associated clinical diagnosis will also be reported as AEs and will be included in the tabulation of AEs described above.

In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table (see Section 6.4.2 of the protocol) will be tabulated by treatment arm for each safety visit time point. In addition to SAEs, a list of the participants with the results: ALT≥3xULN and bilirubin≥2xULN will be provided.

9.5.4 Other Safety Measures

9.5.4.1 12-Lead ECG

The 12-lead electrocardiogram (ECG) findings will be summarized and listed by visit and treatment arm. Corrected QTc intervals will also be summarized by category for change from baseline: <30, ≥30 to <60, and ≥60 (described in table of ECG values of potential clinical importance below) by treatment group at each scheduled visit and for the maximum post baseline values. QTc interval is reported in CRF using one of the reporting methods, Bazett and Fridericia, and is denoted here by QTcB and QTcF, respectively.

Table 1. ECG Values of Potential Clinical Importance

ECG Parameter (QTcB/QTcF)	Potential Clinical Importance Range
Increase from baseline	<30
Increase from baseline	≥30 to <60
Increase from baseline	≥60

In addition, the number (percentage) of participants with ECG values recorded as meeting AE criteria will be tabulated by severity and the relationship to study product and compared between treatment arms using the method as described above.

9.5.4.2 Liver Events

Separate summaries will be presented for liver chemistry tests (AST, ALT, ALK PHOS, and bilirubin): Summary of maximum treatment emergent toxicities for oral phase, injection phase and oral+injection; Summary of changes in baseline toxicity to maximum toxicity for oral phase, injection phase and oral+injection.

By-subject listing of liver events and time of event relative to treatment will be produced. Box plots of liver chemistries (AST, ALT, ALP, and bilirubin) by treatment arm and visit. Scatter plots of maximum liver chemistries during oral (injection phase or oral+injection) phase vs. baseline. Matrix plot of maximum of liver chemistries on-treatment in oral, injection, or oral+injection phase will all be generated.

Kaplan-Meier plot of the time to first occurrence of grade 1 or greater elevation in ALT/AST will be generated by treatment arm during the oral, injection or oral+injection phase.

In addition, the number (percentage) of participants with liver chemistry values recorded as meeting AE criteria will be tabulated by severity and the relationship to study product and compared between the treatment arms as described above.

9.5.5 Safety Endpoint

Primary safety endpoint is the proportion of participants experiencing any Grade 2 or higher clinical AEs or laboratory abnormalities since the initial injection to 12 weeks (8 weeks) after the last injection in Cohort 1 (Cohort 2) among the participants who complete at least one injection to evaluate the safety of the 744 injectable during the injection phase. A secondary safety endpoint is the proportion of Grade 2 or higher clinical AEs or laboratory abnormalities occurred from the initial injection to 76 weeks in both cohorts after last injection among the participants who complete at least one injection to evaluate the safety of the 744 injectable in long term; the proportion of Grade 2 or higher AEs or laboratory abnormalities occurred during the oral phase (Weeks 0-5) among all enrolled participants to evaluate the safety of the oral 744 product; and the proportion of Grade 2 or higher AEs or laboratory abnormalities occurred during the whole study period among the all enrolled participants to evaluate the safety of the oral and injectable product. The proportions of endpoints and the %95 confidence intervals will be estimated for each treatment arm. The 95% CIs will be estimated using Wilson score method[1]. The proportions of endpoints will be compared between the treatment arms using Fisher Exact test.

In addition, the safety endpoint rate might be calculated for each treatment arm and compared between the treatment arms. The safety endpoint rate is the number of the participants who have experienced Grade 2 or higher clinical AEs or laboratory abnormalities during the study period (defined in each safety analysis) divided by the person-time-at-risk throughout the observation period within the study period.

The 95% exact confidence interval of the safety event rate will be calculated for each treatment arm, assuming the rate follows the Poisson distribution. The safety event rate will be compared between the treatment arms using exact Poisson test.

9.5.6 Reasons for Treatment Discontinuation and Early Study Termination

The number and percentage of participants who discontinue the study treatment and who terminate the study early will be tabulated by reasons and the treatment arm separately for the oral phase and the injection phase by cohort and in aggregate.

9.6 Tolerability

To assess tolerability of 744 LA, the proportion (with 95% CI) of subjects who terminate from receiving injections prior to the full course due to AEs, intolerability of injection, frequency of injections, or burden of procedures related to injections out of those subjects that received at least one injection by cohort and treatment arm will be provided. The proportion will be compared between the treatment arms by cohort and in aggregate using Fisher Exact test.

9.7 Pharmacokinetics

Plasma GSK1265744 concentration-time data will be analyzed by noncompartmental methods using WinNonlin Professional 5.2 or higher, Phoenix (Pharsight Corporation) or comparable software. Individual plasma PK parameters for each injection interval will be determined which include the area under the plasma concentration time curve over the dosing interval ($AUC(0_{-\tau})$), maximum observed concentration (C_{max}), time to maximum observed concentration (tmax), concentration at the end of the dosing interval (C_{τ}), apparent terminal phase half-life for 744LA administration ($t_{½}$) and lambda z as a measure of absorption rate constant (λ_z) if data allow among the participants in the 744 arm. The pharmacokinetic parameters will be generated by the scientist from HPTN Core Laboratory.

The summary statistics of pharmacokinetic parameters, $AUC_{(0-\tau)}$, C_{max}, and C_{τ}, will be presented by injection. The means of the pharmacokinetic parameters (after log-transformation) and their 95% CIs will be displayed by visit weeks and cohort. The pharmacokinetic parameters, $AUC_{(0-\tau)}$, C_{max}, and C_{τ} in different injection intervals will be compared using paired t-test if the data or log transferred data appear to be normally distributed and using Wilcoxon signed rank test if the data or log transferred data are not normally distributed.

Time to steady state will also be assessed by comparing plasma concentration, C_{τ}, at Week 41 (following third injection) to previous C_{τ} concentrations at Weeks 17 and 29 (at Weeks 17, 25, and 29) in Cohort 1 (Cohort 2). General estimation equation (GEE) regression model will be used to test any difference in the concentration over time and a trend.

9.7.1 Association between Pharmacokinetics and Baseline Characteristics

To evaluate differential pharmacokinetics of 744LA in participants by age, gender, race, ethnicity, weight, body mass index (BMI), and smoking status, we will use GEE regression model to account the correlations of the PK parameters following three injections in Cohort 1 or five injections in Cohort 2. The analysis will be performed separately for each cohort. The associations between the PK parameters and the predictors will be tested in univariate models (include one predictor in each model) and

in a multivariate model (include all predictors). Each model will be adjusted for sites (US vs. Non-US sites) by cohort.

9.8 Study Medication Satisfaction Questionnaire

The Study Medication Satisfaction Questionnaire (SMSQ) will also be used to assess subject tolerability and satisfaction to the study medication in this trial. The SMSQ is a modified version of the current HIV Treatment Satisfaction Questionnaire (HIVTSQ) that does not include questions pertaining to treatment but rather study medication. The SMSQ is a 12-item self-reported scale that measures overall satisfaction with medication, general satisfaction/clinical, satisfaction with lifestyle/ease, and each individual satisfaction. This study uses the SMSQs (status version) and the SMSQc (change version).

The SMSQs will be administered at the following time points: Week 6, Week 18, and Week 30 in Cohort 1 and Weeks 6, 10, 18, 26, and 34 in Cohort 2. The SMSQc will be administered at Week 18 in Cohort 1 and Week 10 in Cohort 2.

For each question the responses will be summarized by the proportion of participants reporting the response on the Likert scale out of all those that answered the question at visit by the treatment arm. An overall treatment satisfaction score will be calculated for each participant at each visit. To evaluate the participants' experience of the medication with injection comparing to the experience of medication with tablets during the first 4 weeks of the study, the score derived from SMSQc will be summarized by treatment arm and compared between the treatment arms using t-test and using the linear regression model to adjust for site effect (US sites vs. Non-US sites). To evaluate the participants' experience of the medication with injection, the scores derived from SMSQs will be summarized by treatment arm and visit and compared between the treatment arms over time using GEE model to account for the correlations of the scores over time and will be evaluated the changes over time within the treatment arms. The analyses will be done by Cohort and in aggregate.

9.9 Acceptability Questionnaire

Baseline acceptability questionnaire (BAQ) will be administered at baseline Week 0 visit in both cohorts. Follow-up acceptability questionnaire (FAQ) will be administered at Weeks 6, 18, and 30 in Cohort 1; at Weeks 6, 10, 18, 26, and 34 in Cohort 2.

The scores will be derived from the items in BAQ/FAQ at each visit and then will be compared between the treatment arms. The scores derived from BAQ will be summarized and compared between the treatment arms using t-test and using the linear regression model to adjust for site effect (US sites vs. Non-US sites). The scores derived from FAQ will be summarized and compared between the treatment arms using GEE model to account for the correlations of the scores over time and will be evaluated the changes over time within the treatment arms. The data will be analyzed by cohort and in aggregate.

9.10 Sexual Risk Behaviors

To assess the 744LA effect on sexual risk behavior by change from enrollment during the study period, the behavioral questionnaire (BQ) will be administered at the baseline (at

enrollment date) and at each injection visit week (Weeks 5, 17, 29 in Cohort 1 and 5, 9, 17, 25, 33 in Cohort 2) and tail visit weeks 41, 53, 65 and 77.

We will first assess whether or not there is any change in the sexual risk behavior at Week 5 from enrollment within each treatment arm and whether or not the change differs between the 744LA arm and the placebo arm. Then we will assess whether or not there is any change in the sexual risk behavior during the injection phase from the baseline (at Week 5) within each treatment arm and whether or not the change differs between the treatment arms over time using GEE model. The sexual risk behavior variables, such as the number of sexual partners, the number of total sexual acts, the episodes of unprotected anal and/or vaginal intercourse, the number of unprotected sexual acts with HIV seropositive partner(s) in the past 3 months, are as the outcomes and are assumed with a negative binomial distribution. The treatment and time are as covariates. Both analyses will be stratified by gender and adjusted for other demographic variables such as age and race/ethnicity. Robust standard errors will be used to account for within-person correlation. In the second analysis, time is treated as a continuous variable measured in 3 months; a linear and quadratic time and time interactions with the treatment are included in the model to test a linear or a quadratic trend in the self-reporting risk behavior in the past 3 months during the injection phase in each arm and to test the difference between the treatment arms. The data will be analyzed in aggregate.

9.11 HIV Incidence

HIV incidence rate will be calculated as the total number of participants with confirmed HIV infection during study follow-up divided by the person-years accumulated in each arm. 95% CIs will be calculated based on Poisson distribution assumptions. In addition, exact tests based on the Poisson distribution will be used to compare HIV incidence rate between the treatment arms.

9.12 Evaluate the Safety, Tolerability and Pharmacokinetics of 744LA in the Women Who Use Injectable Hormonal Contraception

The safety and tolerability analyses described above will be performed on the subset of female participants who self-report the use of injectable hormonal-based contraception at study entry or at any time during the study period. Proportions of such women meeting safety or tolerability endpoints will be compared a) across treatment arms b) to the women in the 744LA arm who are do not report use of injectable hormonal contraception c) to the overall study population randomized to active GSK1265744. The comparisons in a) are to evaluate the safety and tolerability of the 744LA injection in the women who report use of injectable hormonal-based contraception between the two treatment arms. The comparisons in b) are to evaluate the safety and tolerability of the 744LA injection between the women who report the use of injectable hormonal-based contraception and the women who are do not report the use of injectable hormonal-based contraception. The comparisons in c) are to evaluate the safety and tolerability of the women who report the use of injectable hormonal-based contraception in contrast to the rest of the enrolled participants in the study. All comparisons will be done using the Fisher exact test. The data will be analyzed by cohort and in aggregate.

9.13 Exploratory Analyses

Pharmacokinetics/Pharmacodynamics

The relationship between GSK1265744 PK parameters and demography variables (age, gender, race, ethnicity, weight, BMI, smoking status) or PD endpoints (conversion to HIV-infected status, safety parameters) may be explored.

Pharmacogenomics Analysis

Specific genes may be studied that encode the drug targets, drug mechanism of action pathways, drug metabolizing enzymes, or drug transporters or which may underpin AEs, disease risk, or pharmacokinetics or drug response. These candidate genes may include a common set of absorption, distribution, metabolism, and excretion genes that are studied to determine the relationship between gene variants and pharmacokinetics or safety parameters. In addition, future research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to GSK1265744. The genes that may code for these proteins may also be studied.

A detailed statistical analysis plan will be documented separately once the pharmacogenomics study plan is finalized.

10 SMC REPORTS

10.1 Cohort data will be analyzed and presented separately in all SMC report periods. If appropriate, they will be analyzed jointly in the last SMC report period. Study Conduct Report (SMC Open Report)

10.1.1 List of Tables

- Accrual summary by site and by gender
- Accrual summary and accrual by calendar month and by site
- Specimen collection by pre-specified specimen collection visits and site
- Retention by study visit and by site
- Baseline demographics for total and by site
- Completion of behavioral assessment questionnaire (BQ) by study visit and site
- Completion of Study Medication Satisfaction questionnaire (SMSQ) by study visit and site
- Completion of Baseline Acceptability questionnaire (BAQ) by site and completion of Follow-up Acceptability questionnaire (FAQ) by study visit and site
- Adherence as measured by pill counts during 4 weeks of oral phase by study visit (Weeks 2 and 4) and site

- Adherence as measured by self-report at Week 4 by site
- Completion of injections by study visit and site
- Baseline sexual risk behavior
- Study product holds and earlier discontinuations by site
- Reasons for early discontinuation of study regimen during the oral phase by site
- Reasons for not advancing to injection phase by site
- Reasons for early discontinuation of study regimen during the injection phase by site
- Social harms/impacts summary
- Pregnancy listing

10.1.2 List of Graphs

- Accrual graph by calendar month – total
- Accrual graph by calendar month - by site

10.2 Safety Tables and Graphs (SMC Close Report)

10.2.1 List of Tables

- Permanent discontinuation of study regimen during the oral phase (Weeks 0-5) by treatment arm
- Permanent discontinuation of study regimen during the injection phase (Weeks 5-41) by treatment arm
- Permanent discontinuation of study regimen during the tail phase (Weeks 41-105/109) by treatment arm
- List of early discontinuation of study regimen (reason, study week)
- Grade 3 or higher adverse events by treatment arm during the oral phase (Weeks 0-5)
- Proportion of Grade 2 or higher adverse events by treatment arm during the oral phase (Weeks 0-5)
- Adverse events by severity and relationship to study product during the oral phase (Weeks 0-5)

- Adverse events by MedDRA preferred term ordered by system organ class during the oral phase by treatment arm (Weeks 0-5)
- listing of Grade 3 or above adverse events during the oral phase by treatment arm (Weeks 0-5) with details of the events including severity, relationship to the study product, on-set date, outcome, duration, the enrollment date and days since the enrollment.
- Grade 1 or above AST/ALT by treatment arm during the oral phase (Weeks 0-5)
- Grade 2 or higher adverse events by treatment arm during the injection phase (Weeks 5-41)
- Number and percentage of adverse events by severity and relationship to study product during the injection phase (Weeks 5-41)
- Adverse events by MedDRA preferred term ordered by system organ class during the injection phase (Weeks 5-41)
- Injection site reaction (ISR) adverse events during the injection phase by BMI (above/below median BMI) (Weeks 5-41)
- Grade 1 or above AST/ALT by treatment arm during the injection phase (Weeks 5-41)
- Adverse events by MedDRA preferred term ordered by system organ class during the injection phase (Weeks 5-105/109)
- listing of Grade 3 or above adverse events during the whole injection phase (Weeks 5-81) with details of the events including severity, relationship to the study product, on-set date, outcome, duration, last injection date, and the number of injections prior to the event
- Adverse events by severity and relationship to study product and treatment arm during the whole injection phase (Weeks 5-105/109)
- Grade 1 or above AST/ALT by treatment arm during the whole injection phase (Weeks 5-105/109)
- HIV infection status by study arm
-

10.2.2 List of Graphs

- Kaplan-Meier curves of time to permanent discontinuation by treatment arm (For those who complete the study and currently stay in the study, their time to permanent discontinuation will be censored at the last visit date)
- Box plots of maximum liver chemistries (AST, ALT, ALP, and bilirubin) by treatment arm and visit during oral, injection, and oral+injection phase.

- Scatter plots of maximum liver chemistries during oral, injection, and oral+injection phase vs. baseline.

- Matrix plot of maximum of liver chemistries during the oral, the injection, and the oral+injection phase.

- Shift plot of some laboratory measure at each visit week vs. baseline during the oral, injection, and oral+injection phase.

- Cumulative incidence curve of the time to first occurrence of grade 1 or greater elevation in ALT/AST will be generated by treatment arm during the oral, injection and oral+injection phase.

11 FINAL STUDY REPORT (FSR)

The data will be analyzed by cohort and in aggregate (if it is appropriate).

11.1 Study Population Summary

All study population characteristics will be provided for table and by treatment arm

11.1.1 Lists of Tables

Table 1 Summary of study populations

Table 2 Summary of subject accountability: Study conclusion record

Table 3 Summary of baseline demographic characteristics

Table 4 Summary of baseline risk behavior

Table 5 Summary of baseline concomitant medications

Table 6 Summary of important protocol deviations

Table 7 Summary of exposure to randomized investigational product

11.2 Safety and Tolerability Analysis

11.2.1 Lists of Tables

Table 8 Permanent discontinuation of study regimen by treatment arm (a) during the oral phase, (b) during the injection phase, and (c) during the on-treatment

Table 9 Adverse experiences by MedDRA preferred term and severity (ordered by system organ class) (a) during the oral phase, (b) during the injection phase, (c) during the tail phase, and (d) during the on-treatment

Table 10 Adverse experiences by MedDRA preferred term and severity – including severe, potential life-threatening or fatal events only (a) during the oral phase, (b) during the injection phase, (c) during the tail phase, and (d) during the on-treatment

Table 11 Adverse experiences by MedDRA preferred term and relationship to study product (a) during the oral phase, (b) during the injection phase, (c) during the tail phase, and (d) during the on-treatment

Table 12 Elevation of liver chemistry and other lab test events (a) during the oral phase, (b) during the injection phase, (c) during the tail phase, and (d) during the on-treatment

Table 13 Summary of Injection Site Reaction Characteristics

Table 14 Summary of characteristics of common ISR symptoms

Table 15 Summary of change in laboratory test at follow up from baseline by visit and cohort

Table 16 Summary of ECG values by treatment arm and visit

Table 17 Summary of maximum change in corrected QTc intervals by category for change from baseline

Table 18 Listing of expedited adverse events (EAE) or serious adverse events (SAE) with the details of the events including severity, relationship to study product, time between onset and last injection, number of injections received (if the events occurring after the 1st injection), and a summary of the event

Table 19 Proportion of participants experiencing any Grade 2 or higher clinical AEs and laboratory abnormalities that occur (a) during the oral phase, (b) during the injection phase (c) during the tail phase, and (d) during the on-treatment period

Table 20 The proportion of participants who discontinue the study product for reasons of toxicity, tolerability, or acceptability (a) prior to completion of the full oral phase and (b) prior to completion of the full injection phase.

11.2.2 List of Figures

Figure 1 Kaplan-Meier curves of time to permanent discontinuation by treatment arm (For those who complete the study and currently stay in the study, their time to permanent discontinuation will be censored at the last visit date)

Figure 2 Kaplan-Meier curves of time to permanent discontinuation by treatment arm (For those who enter the injection phase and currently stay in the study, their time to permanent discontinuation will be censored at the last visit date)

Figure 3 Shift scatter plot of some laboratory measures at each visit week vs. baseline

Figure 4 Box plots of maximum some laboratory measures (AST, ALT, ALP, total bilirubin, CPK, Creatinine, Creatinine clearance) elevation from baseline by treatment arm and phase

Figure 5 Scatter plots of maximum liver chemistries (a) during the oral (b) during the injection (c) during the tail phase and (d) during the on-treatment phase vs. baseline.

Figure 6 Matrix plot of maximum of liver chemistries (a) during the oral (b) during the injection (c) during the tail phase and (d) during the on-treatment phase

Figure 7 Cumulative incidence plot of the time to first occurrence of grade 1 or greater elevation in ALT/AST will be generated by treatment arm (a) since the enrolment date and (b) since the first injection date

11.3 Pharmacokinetic and Other Secondary Analyses

11.3.1 List of Tables

Table 21 Summary of pharmacokinetic parameters by injection

Table 22 Assess the time to steady state of the plasma drug concentration, $C\tau$

Table 23 Associations of sex at birth (or BMI) with pharmacokinetic parameters

Table 24 Change in sexual risk behavior (number of sexual partners) from baseline

Table 25 HIV incidences during the study

Table 26 Reported pregnancies by treatment arm and cohort

Table 27 The proportion of women experiencing any Grade 2 or higher AEs (a) prior to completion of the full oral phase and (b) prior to completion of the full injection phase --- among the women who use any injectable hormonal contraception (combined cohort)

Table 28 The proportion of the women who discontinue the study product for reasons of toxicity, tolerability, or acceptability (a) prior to completion of the full oral phase and (b) prior to completion of the full injection phase—among the women who use any injectable hormonal contraception

Table 29 Summary of pharmacokinetic parameters by injection and cohort —among the women who use any injectable hormonal contraception

11.3.2 List of Figures

12 ATTACHMENTS

- The tables shell: the tables listed in Section 11.
- The figures shell: the figures listed in Section 11.

13 REFERENCE

1. Agresti A, Coull BA. Approximate Is Better than “Exact” for Interval Estimation of Binomial Proportions. *Am Stat*. 1998;52(2):119–126.

Appendix

Definition of Derived Variables and Study Populations

Study Populations:

Randomized population: randomized=1 if Screnr = 1 (Form SO-1 006, screening outcome)

Oral safety analysis population: randomized=1 and PCpdn>0 and PCpbrp="No", or PCpdn>Pcnumpil if PCpbrp="Yes" (Form PC-1 134, Pill count)

Primary/Injectable safety analysis population: randomized=1 and laingiv=1 for week5 (Form IA-1 126, Injection administration)

Derived Variables:

BMI=weight (in kg)/ height(in cm)*height(in cm) (Form LLR-1152, Local Laboratory Results)

Algorithm of defining the phase for AEs

The phase (oral or injection) of AEs was determined based on the AE on-set date and the first injection date as follows.

For AEs with a complete onset date (no missing on day, month, or year)

1. If the AE onset date is before of the first injection date, then the phase of the AE is oral.
2. If the AE onset date is after the first injection date, then phase of the AE is injection.
3. If the AE onset date is on the same data as the first injection date, then:
   a. If the AE is Injection site reaction, then the phase of the AE is injection.
   b. If the AE is not Injection site reaction, then the phase is oral.

For the AEs with an incomplete onset date (missing day, day is not mandated)

1. If the onset date is before the first injection date determined by the month and the year of the onset date, then the phase is oral.
2. If the onset date of the AE is after of the first injection date determined by the month and the year of the onset date, then the phase is injection.
3. If the month and year in the AE onset date match to the month and year in the first injection date, then:
   a. the sites determined whether the AE occurred before or after the first injection.
   b. If the sites could not determine, PI determined which phase the AE should be.