**Statistical Analysis Plan**

**Official Title of Study:** A Phase 2, Double-Blinded, Randomized, Placebo-Controlled, Dose-Escalation Study to Examine the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of ISIS 505358 in Treatment-Naïve Patients With Chronic HBV Infection

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PPD

**PPD Biostatistics and Programming**

Statistical Analysis Plan (SAP) Client Approval Form

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Date *(DD-MMM-YYYY)*

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PPD

**PPD Biostatistics and Programming**

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*Ionis Pharmaceuticals*

***ISIS 505358-CS3***
***Protocol Amendment 2 – Hong Kong***
***Protocol Amendment 3 - Korea***

# *A Phase 2, Double-Blinded, Randomized, Placebo-Controlled, Dose-Escalation Study to Examine the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of ISIS 505358 in Treatment-Naïve Patients with Chronic Hepatitis B Virus Infection*

***12JUL2019***

Statistical Analysis Plan

**Version 3.0**

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## List of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | Adverse event |
| ALC | Absolute leukocyte count |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| ANC | Absolute neutrophil count |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransaminase |
| AUC | Area under the plasma concentration-time curve |
| Anti-HBe antibody | Antibody to HBV e antigen |
| Anti-HBs antibody | Antibody to HBV surface antigen |
| BLQ | Below the limit of quantification |
| BUN | Blood urea nitrogen |
| $C_{max}$ | Maximum observed drug concentration |
| CHB | Chronic hepatitis B |
| CI | Confidence interval |
| CRO | Contract research organization |
| CV | Coefficient of variation |
| DAIDS | Division of AIDS |
| DNA | Deoxyribonucleic acid |
| DSMB | Data safety monitoring board |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| FAS | Full analysis set |
| GGT | Gamma-glutamyl transferase |
| HBV | Hepatitis B virus |
| HBeAg | Hepatitis B e antigen |
| HBsAg | Hepatitis B surface antigen |
| HCC | Hepatocellular cancer |
| HIV | Human Immunodeficiency virus |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IXRS | Interactive voice/internet response system |
| LCRIS | Local cutaneous reaction at injection site |
| LDH | Lactate dehydrogenase |
| LOCF | Last observation carried forward |
| LS | Least squares |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| n/a | Not applicable |
| PBMC | Peripheral blood mononuclear cell |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| PT | Preferred term |
| PT | Prothrombin time |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |

| | |
|---|---|
| SD | Standard deviation |
| SOC | System organ class |
| Study Day 1 | Defined as the first day Study drug product is administered to the patient |
| Study Drug | ISIS 505358 or Placebo |
| TEAEs | Treatment-emergent AEs |
| Tenofovir | Tenofovir disoproxil fumarate |
| $T_{max}$ | Time taken to reach $C_{max}$ |
| ULN | Upper limit of the laboratory reference range |
| WBC | White blood cell |
| WHO-DD | World Health Organization drug dictionary |

## 1. Introduction

In general, the purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

This is a Phase 2, double-blinded, randomized, placebo-controlled, dose-escalation study to examine the safety, tolerability, pharmacokinetics (PK), and antiviral activity of ISIS 505358 in treatment-naïve patients with chronic hepatitis B virus (HBV) infection.

Chronic hepatitis B (CHB) is a spectrum of disease characterized by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood or serum for longer than 6 months. The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated liver disease, end-stage liver disease, Hepatocellular cancer (HCC) and death.

ISIS 505358 is antisense inhibitor that is designed to inhibit the synthesis of viral proteins (e.g., HBsAg, hepatitis B e antigen [HBeAg]) without having a direct effect on covalently closed circular deoxyribonucleic acid (DNA) or integrated HBV DNA. Treatment of CHB patients with ISIS 505358 will permit examination of whether reduction of viral proteins allows resumption of a host immune response against HBV virus and infected cells and can induce HBsAg and/or HBeAg seroclearance leading to sustained suppression of HBV replication after cessation of all treatments for CHB.

## 2. Objectives

### 2.1. Primary Objectives

To examine the safety and tolerability of ISIS 505358 administration to treatment- naïve patients with chronic HBV infection.

### 2.2. Secondary Objectives

- To examine the effects of ISIS 505358 administration on plasma HBV DNA concentration
- To examine the effects of ISIS 505358 administration on serum HBsAg concentration

- To examine the effect of ISIS 505358 administration on serum HBeAg concentration in the patients who were HBeAg positive at Baseline
- To assess plasma PK of ISIS 505358 in patients with chronic HBV infection
- To describe the safety and tolerability of tenofovir (and entecavir if administered) therapy following conclusion of ISIS 505358 administration

### 2.3. Exploratory Objectives

- To describe the rate of seroconversion of patients to antibody to HBV surface antigen (anti-HBs antibody) positivity during treatment with ISIS 505358 and then during subsequent treatment with tenofovir (or entecavir)
- To describe the seroconversion of HBeAg positive patients to antibody to HBV e antigen (anti-HBe antibody) positivity during treatment with ISIS 505358 and then during subsequent treatment with tenofovir (or entecavir)
- To explore the effect of prior ISIS 505358 exposure on the plasma concentrations of tenofovir (and entecavir) administered after the conclusion of ISIS 505358 administration
- To explore antiviral activity, safety/tolerability, and PK during concurrent treatment with ISIS 505358 and nucleos(t)ide analogue (i.e., tenofovir or entecavir)

## 3. Investigational Plan

### 3.1. Overall Study Design and Plan

This study examines the effects of ISIS 505358 or placebo (3:1 randomization) administered subcutaneously to treatment-naïve patients who are chronically infected with HBV and the effects of subsequent nucleos(t)ide analogue treatment of these patients. Three (3) ISIS 505358 dose levels will be evaluated through the treatment of 3 sequential cohorts of 8 patients each:

- Cohort 1 (150 mg ISIS 505358 or placebo)
- Cohort 2 (300 mg ISIS 505358 or placebo)
- Cohort 3 (450 mg ISIS 505358 or placebo) (note: cohort was studied as 300 mg ISIS 505358 or placebo based on antiviral activity observed in Cohort 2)
- Cohort 4 (300 mg ISIS 505358 or placebo with stable nucleos(t)ide analogue (i.e., tenofovir or entecavir) regimen)

In these cohorts, 6 patients will be randomized to treatment with ISIS 505358 and 2 patients to treatment with placebo. Patients enrolled into the study may be either HBeAg positive (+) or negative (-).

The Study will consist of Screening, Treatment, and Post-Treatment Follow-up Periods. Please refer to the Schedule of Procedures in Appendix 14.1.

For each patient in Cohorts 1-3, Study Drug (ISIS 505358 or placebo) will be administered twice in Weeks 1 and 2 (on Days 1, 4, 8, and 11), and then once weekly during Weeks 3 and 4 (i.e., on Days 15 and 22). They will additionally report to the Study Center for assessment on Study Days 2, 23, and 29. After these assessments, all patients will then commence chronic daily treatment with tenofovir disoproxil fumarate (tenofovir) (entecavir if judged more appropriate by the patient or Investigator) for 6 months. Patients are to return to the Study Center for follow-up visits on Study Days 36, 57, 85, 113, and 211. The final study visit will be Study Day 211. Continuation of nucleos(t)ide analogue after discontinuation from this study will be the decision of the patient in consultation with their physician.

The target size of Cohort 4 is approximately 8 patients, but the size may range from 4 to > 8 depending upon availability of participants. Each patient randomized into Cohort 4 is expected to continue their ongoing nucleos(t)ide analogue regimen and be treated with Study Drug by the above schedule for Cohorts 1–3. After Day 22, the patients are expected to continue their ongoing nucleos(t)ide analogue regimen and be followed until Day 211. On Day 29, the effects of Study Drug treatment will be assessed.

An independent Data and Safety Monitoring Committee (DSMB) will participate in the review of the study results and in the dose-escalation decisions.

Approximately 24 patients will be treated with Study Drug in this study. Additional patients may be treated due to difficulties of coordinating screening and enrollment from multiple sites and/or to replace patients that discontinue from cohorts before Day 29 for non-adverse event reasons but the actual number treated will not exceed 32.

## 3.2. Study Endpoints

### 3.2.1. Primary Endpoints

The safety endpoints include:

- Adverse events

- Clinical laboratory tests (e.g., serum chemistry, hematology, urinalysis, coagulation, complement, antibodies, pregnancy test for women with childbearing potential)
- Vital signs and body weight
- Physical examination
- Electrocardiogram (ECG)
- Concomitant medication usage

There is no primary efficacy endpoint.

### 3.2.2. Secondary Endpoints

The efficacy endpoints include:

- Change from Baseline to Day 29 in plasma HBV DNA concentration
- Change from Baseline to Week 31 in plasma HBV DNA concentration
- Change from Baseline to Day 29 in serum HBsAg concentration
- Change from Baseline to Week 31 in serum HBsAg concentration
- Proportion of patients with HBsAg loss at Day 29 and at Week 31
- Change from Baseline to Day 29 and to Week 31 in serum HBeAg concentration in patients who were HBeAg positive at Baseline
- Proportion of patients with HBeAg loss at Day 29 and at Week 31 in patients who were HBeAg positive at Baseline
- Plasma PK of ISIS 505358 in patients with chronic HBV infection

### 3.2.3. Exploratory Endpoints

- Proportion of patients with seroconversion to anti-HBs antibody positivity at Day 29 and at Week 31
- Proportion of patients with seroconversion to anti-HBe antibody positivity at Day 29 and at Week 31 in patients who were HBeAg positive at Baseline
- Plasma concentrations of tenofovir and entecavir

### 3.3. Treatments

Study Drug (ISIS 505358 or placebo) will be administered by subcutaneous (SC) injection by trained study center personnel. The recommended sites for injection are the abdomen, upper arm, and thigh. Eligible patients will report to the Study Center for treatment with Study Drug on Study Days 1, 4, 8, 11, 15, and 22. They will additionally report to the Study Center for assessment on Study Days 2, 23, and 29. Patients in Cohort 4 are expected to continue to take their ongoing nucleos(t)ide analogue therapy during this period.

The dose levels (150, 300, and 450 mg) are selected from a previous study, ISIS 505358-CS1, a Phase 1, blinded, placebo-controlled, dose escalation study designed to assess the safety, tolerability and pharmacokinetics of single and multiple doses of ISIS 505358 administered to healthy patients.

## 4. General Statistical Considerations

Descriptive summary statistics including n, mean, median, standard deviation (SD), interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% type I error rates.

For data summaries and statistical analyses, the placebo patients from all 3 cohorts will be pooled.

### 4.1. Sample Size

There is no statistical rationale for the selected sample size of 8 patients per cohort. The sample size was based on prior experience with other members of the drug class to ensure an adequate initial assessment of the safety, tolerability, and PK of ISIS 505358 while minimizing the number of patients unnecessarily exposed to the drug.

### 4.2. Randomization and Blinding

Patients will be randomized prior to the first dose of Study Drug (ISIS 505358 or placebo), after all screening assessments have been completed and after the Investigator has verified that they are eligible. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

The Investigator or designee will obtain the patient’s identification number and cohort, and Study Drug kit number from an Interactive Voice/Internet Response System (IXRS).

The system will randomize eligible patients 3:1 to receive ISIS 505358 or placebo, respectively.

A permuted block schedule will be used for the randomizations. The Sponsor's Quality Assurance department or designee will hold a copy of the randomization lists generated by the IXRS vendor.

This is a double-blind study: all patients, study monitors, Study Center personnel and contract research organization (CRO) personnel will be blinded to Study Drug assignment (ISIS 505358 or placebo) throughout the study. The DSMB may be unblinded when reviewing safety and tolerability results. Sponsor and contract personnel supporting the DSMB, and not in communication with Investigators and/or investigational site staff, may also be unblinded. Every reasonable attempt should be made to complete the early termination study procedures and observations prior to unblinding, as knowledge of the treatment group could influence patient assessment.

### 4.3. Analysis Set

#### 4.3.1. All Enrolled Set

The All Enrolled Set will include all patients who signed the informed consent form (ICF) and enrolled into the study.

#### 4.3.2. Safety Set

The Safety Set will include all randomized patients who received at least 1 dose of ISIS 505358 or placebo. When the Safety Set is used, patients will be analyzed according to the treatment they actually received. Patients who receive any dose of ISIS 505358 will be included in the ISIS 505358 group and patients who did not receive any dose of ISIS 505358 will be included in the placebo group in each cohort, regardless of their randomized treatment.

The Safety Set will be used for all safety related analyses such as AE, concomitant medication, laboratory tests, vital signs and ECG.

#### 4.3.3. Full Analysis Set

The Full Analysis Set (FAS), which represents the practically-feasible Intent-to-treat (ITT) population, will include the subset of the Safety Set with a Baseline and at least 1 post-Baseline plasma HBV DNA concentration. The FAS will be used for all efficacy

endpoints. When the FAS is used, patients will be analyzed according to the randomized treatment.

#### 4.3.4. Per Protocol Set

The Per-Protocol (PP) Set will include the subset of the FAS who have:

- received at least 5 doses of ISIS 505358 or placebo during the 4-week Treatment Period
- had plasma HBV DNA concentration measure at Day 29, and
- had no significant protocol deviations that would be expected to affect efficacy assessments

The PP Set will be used for all efficacy endpoints.

#### 4.3.5. Pharmacokinetic (PK) Population

The PK Population will include patients who were randomized, received at least 1 dose of study drug, and had at least 1 valid PK metric. In the PK analyses, patients will be analyzed according to the treatment they actually received.

## 5. Patient Disposition

### 5.1. Disposition

Patient disposition includes the number and percentage of patients for the following categories: patients in each of the study populations, patients discontinued from study treatment, primary reason to discontinue from study treatment, patients discontinued from the study, and primary reason for study discontinuation. All percentages will be based on the number of patients randomized using the All Enrolled Set.

Screen failures with reasons for screen failure will be summarized using frequency counts and percentages of All Enrolled Set.

A listing will present data concerning patient disposition. Screen failures and reasons for screen failure will be presented in a listing. All patients enrolled will be included in the summary of patient disposition.

Reasons for treatment discontinuation will be collected on eCRF with the following categories:

- Adverse event
- Death

- Lack of efficacy
- Lost to follow-up
- Non-Compliance with Study Drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol violation
- Study terminated by sponsor
- Technical problem
- Withdrawal by subject
- Protocol defined stopping criteria
- Other

Reasons for study discontinuation will be collected on eCRF with the following categories:

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Non-Compliance with Study Drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol violation
- Recovery
- Trial screen failure
- Study terminated by sponsor
- Technical problem
- Withdrawal by subject

- Other

Reasons for screen failure will be collected on eCRF with the following categories. A patient may have more than one screen failure reason:

- Did not meet inclusion/exclusion criteria
- Adverse event
- Study closed/terminated
- Investigator discretion
- Withdrew consent
- Screened but enrollment target reached prior to enrollment

### 5.2. Protocol Deviations

Besides the protocol deviations reported by clinical teams, dosing errors will be identified after database lock and unblinding. Patients who receive a wrong study drug (ISIS 505358 or placebo) will be considered as having dosing errors and therefore protocol deviations. Significant protocol deviations are departures from the protocol that impact patient safety or data integrity. All significant protocol deviations will be documented and reviewed by the PPD project team and approved by the sponsor. Final approval will determine which patients will be excluded from the Per-Protocol Set due to significant protocol deviations.

The number and percentage of patients with protocol deviations will be summarized in a table for the Safety Set. The number and percentage of patients with significant protocol deviations will be summarized as well. A listing will be generated for protocol deviations.

## 6. Demographics and Baseline Characteristics

Baseline ECG will be the average of the triplicate taken on Day 1 Pre-dose, if only 1 or 2 assessments are available, the single assessment or average of the 2 assessments will be used.

Baseline creatinine will be the average of all measurements taken between Screening and Day 1 Pre-dose.

For other assessments, baseline will be the last non-missing measurement prior to the first dose of Study Drug.

### 6.1. Demographics

Demographic and baseline characteristics will be summarized descriptively by treatment group for the Safety Set. Baseline demographic data to be evaluated will include age, sex, height, weight, and other parameters as appropriate.

Only year of birth will be collected on eCRF. A patient's age is calculated using the year part of ICF – year of birth +1.

### 6.2. Baseline Disease Characteristics

Baseline disease characteristics will be summarized by each treatment group, including measurement of HBsAg, HBeAg, HBV DNA, HBV drug binding sites DNA sequence, HBsAg genotype, anti-HBs antibody, anti-HBe antibody, hepatitis D antibody, hepatitis C antibody, human immunodeficiency virus (HIV) antibody, Alpha-fetoprotein, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin for the Safety Set.

### 6.3. Medical History

#### 6.3.1. General Medical History

General medical history will be coded using the Medical Dictionary for Regulatory Activities® (MedDRA) Version 19.1 or higher. General medical history will be listed for all randomized patients.

Substance use (smoking history and alcohol history) will be presented in a listing for all randomized patients.

#### 6.3.2. Disease-Specific History

Disease specific history will be summarized by each treatment group for any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before signing the ICF).

### 6.4. Inclusion and Exclusion Criteria

A listing will present inclusion/exclusion criteria for all patients enrolled.

## 7. Treatments and Medications

### 7.1. Prior and Concomitant Medications

Any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing the ICF and last post-treatment visit will be collected on the eCRF.

Entecavir and tenofovir are considered concomitant medications in this study. In Cohort 4, patients should be on stable tenofovir or entecavir therapy prior to Screening and their nucleos(t)ide analogue usage should be in accordance with the recommendations contained in their respective region-specific prescribing information. For all cohorts, each patient's nucleos(t)ide analogue usage will be recorded in each patient's eCRF.

A prior medication is defined as any medications that is ended prior to the date of first dose of study drug. Medications initiated after the first dose of study drug, or initiated prior to the first dose of study drug and continued after the first dose of study drug will be counted as concomitant medications. A medication cannot be determined as prior or concomitant medication due to partially or completely missing start/stop date will be counted as both prior and concomitant medication.

All medications will be coded according by drug class and preferred term (PT) using the World Health Organization drug dictionary (WHO-DD) version July 2016 or later. The number and percentage of patients taking prior and concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) level 1 and 2 term and PT for each treatment group in the Safety Set. By-patient listings will also be presented for prior and concomitant medications.

### 7.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing the ICF and last post-treatment visit. Concomitant procedures will be presented in a data listing in the Safety Set.

### 7.3. Extent of Exposure

Treatment duration and amount of Study Drug received will be summarized by treatment group. An overall summary of drug exposure will be presented including total amount of dose taken (in mg), total number of dose taken, and number and percentages of patients who completed the treatment for each treatment group in the Safety Set. Dosing data will also be presented in a by-patient listing.

## 8. Efficacy Analysis

There are no formal hypotheses in this study; therefore, all the efficacy endpoints will be summarized using descriptive statistics. Efficacy analyses for comparison between ISIS 505358 groups and the pooled placebo group will be performed in an exploratory manner. All efficacy evaluations will be conducted using the FAS and PP analysis sets unless otherwise specified.

The main efficacy analysis will be the changes from Baseline to Day 29 (1-week after last dose of Study Drug) for plasma HBV DNA and serum HBsAg, and change from Baseline to Day 29 in serum HBeAg concentrations for patients who were HBeAg positive at Baseline. These concentrations will be logarithmic transformed with base 10 in this analysis. The last observation carried forward (LOCF) method will be used to impute missing values in this analysis. Comparison between ISIS 505358 and pooled placebo will be performed for each dose level, separately, using an analysis of covariance (ANCOVA) model with baseline as a covariate, and treatment group as a factor. For each of the 3 comparisons, if data departs substantially from normality, the Wilcoxon Rank Sum test will be used.

Additional efficacy analyses will include:

- Changes from Baseline to Week 31 in plasma HBV DNA, serum HBsAg, and changes from Baseline to Week 31 in serum HBeAg concentrations for patients who were HBeAg positive at Baseline. These concentrations will be logarithmic transformed with base 10. Comparison between the ISIS 505358 and placebo treatment groups will be performed using an ANCOVA model with baseline value as a covariate, and treatment group as a factor (if data departs substantially from normality, the Wilcoxon Rank Sum test will be used).
- Proportions of patients with at least 1 logarithmic reduction in plasma HBV DNA, serum HBsAg, and serum HBeAg concentrations (for patients who were HBeAg positive at Baseline) at Day 29 and Week 31 by treatment group. Responder analysis with other response thresholds (e.g., 0.5, 1.5, and 2.0 logarithmic reduction) will also be conducted. Comparison between ISIS 505358 and placebo treatment groups will be performed using the Pearson's Chi-square test or Fisher exact test as appropriate.

Exploratory analyses:

- Proportion of patients with seroconversion to anti-HBs antibody positivity at Day 29 and Week 31. Comparison between ISIS 505358 and placebo treatment groups will be performed using the Pearson's Chi-square test or Fisher exact test as appropriate.

- Proportion of patients with seroconversion to anti-HBe antibody positivity at Day 29 and Week 31 in patients who were HBeAg positive at Baseline. Comparison between ISIS 505358 and placebo treatment groups will be performed using the Pearson's Chi-square test or Fisher exact test as appropriate.

## 9. Safety Analysis

The safety analyses will be conducted on the Safety set.

Patient incidence rates of treatment-emergent AEs (TEAEs) will be tabulated using the MedDRA Terminology dictionary by system organ class (SOC) and PT. Tables of "on-study" deaths, serious and other significant TEAEs, including early withdrawals due to TEAEs, will also be provided.

All TEAEs, all TEAEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Laboratory tests including hematology, chemistry panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug administration, as appropriate.

Vital signs and ECG measures will be tabulated by treatment group. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group. By-patient listings will also be presented for vital signs and ECG measurements.

### 9.1. Adverse Events

Adverse events will be coded using the MedDRA Version 19.1 or higher. All AEs will be presented in a by-patient listing. TEAEs are AEs that occur after administration of the first dose of any study drug and through the end of the study.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

1 If the stop date has month and year but day is missing, the last day of the month will be imputed

2 If the stop date has year, but day and month are missing, the 31st of December will be imputed

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the

imputed date instead. If the stop date of an AE is completely missing, then this event will be regarded as ongoing and will be included in the summary table.

Adverse events with start dates that are completely or partially missing will be imputed as follows:

1. If the start date has month and year but day is missing
    a. If the onset month and year are same as that of first dose date, the first dose date will be used instead. If the onset month and year are different from that of the first dose date, then the first day of the month will be used.
    b. After imputation, the imputed dates will be compared against the stop date. If this date is later than the stop date (possibly imputed), then the stop date will be used instead
2. If the start date has year, but day and month are missing
    a. If the onset year is same as that of first dose date, then the first dose date will be used instead
    b. If onset year is different than that of the first dose date, the 1st of January of the year will be imputed.
    c. After the imputation, the imputed dates will be compared against the dose stop date. If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the start date of an AE is completely missing, then it is imputed with the first dose date.

### 9.1.1. Incidence of Adverse Events

Patient incidence rates of all TEAEs will be tabulated by MedDRA SOC and PT.

All TEAEs, all TEAEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Summaries of the total number of TEAEs and the number and percentage of patients with at least 1 TEAE will be provided by treatment group. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the Safety Set.

A summary of TEAEs will also be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the

lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in an alphabetical order.

### 9.1.2. Relationship of Adverse Events to Study Drug

The relationship of AEs to the study drug is characterized as: related, possible, unlikely/remote, or not related. Missing relationship will be considered as related.

Related AEs are defined as those with relationship to the study drug being related or possible. Related TEAEs will be summarized in a table.

### 9.1.3. Severity of Adverse Event

The event's severity is graded according to the Division of AIDS (DAIDS) Table for Grading Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014 except for responses at subcutaneous injections sites. Responses at injection sites will be graded according to the mild, moderate, and severe criteria defined below. As noted in the DAIDS criteria, clinical AEs not specifically identified in the table are to be characterized by 1 of the following:

**Grade 1 (Mild):** Symptoms causing no or minimal interference with usual social and functional activities

**Grade 2 (Moderate):** Symptoms causing greater than minimal interference with usual social and functional activities

**Grade 3 (Severe):** Symptoms causing inability to perform usual social and functional activities

**Grade 4 (Potentially Life Threatening):** Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability or death

Missing severity will be presented in a separate category in the summary tables by severity.

### 9.1.4. Serious Adverse Events (SAE)

The number and percentage of patients experiencing at least 1 treatment-emergent SAE will be summarized by MedDRA SOC and PT. Drug-related treatment-emergent SAEs will be summarized similarly.

In addition, a by-patient listing of the SAEs with narratives will be presented.

### 9.1.5. Adverse Events Leading to Study Drug Discontinuation

The number and percentage of patients experiencing at least 1 AE resulting in discontinuation of study drug will be summarized by MedDRA SOC and PT. A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented. All TEAEs resulting in discontinuation of the study drug will be displayed.

### 9.1.6. Local Cutaneous Reactions at Injection Sites (LCRIS)

The following MedDRA PTs are determined by the Sponsor's Pharmacovigilance personnel to represent the local cutaneous reaction at the injection site:

- Injection site erythema
- Injection site swelling
- Injection site pruritus
- Injection site pain
- Injection site tenderness

Only events that start on the day of injection and persist for at least two days, i.e. event onset date on the day of injection and resolution date not on the day of injection or the day after the injection, will be included. Events with onset date on the day of injection and missing resolution date will also be included.

The number and percentage of patients in each treatment group experiencing LCRIS will be tabulated.

Percentage of injections leading to local cutaneous reactions at the injection site will also be summarized. Percentage of injections leading to local cutaneous reactions will be calculated for each patient as (A/B) ×100, where A is the number of injections with a local cutaneous reaction at the injection site, and B is the total number of injections.

### 9.1.7. Flu-like Reactions

The following MedDRA PTs are determined by the Sponsor's Pharmacovigilance personnel to be the flu-like reactions:

- Influenza like illness
- Pyrexia (or feeling hot or body temperature increased) plus at least two of the following symptoms:
    - Chills
    - Myalgia
    - Arthralgia

Only events that start on the day of injection or the day after injection will be included.

The number and percentage of patients in each treatment group experiencing flu-like reactions will be tabulated.

Percentage of injections leading to flu-like reactions will also be summarized. Percentage of injections leading to flu-like reactions will be calculated for each patient as (A/B) ×100, where A is the number of injections associated with a flu-like reaction, and B is the total number of injections.

#### 9.1.8. Death

A listing of deaths will be presented. All deaths collected in the CRF will be displayed.

### 9.2. Clinical Laboratory Evaluations

Laboratory test results will be summarized according to the scheduled sample collection time points. Change and percentage change from baseline will also be presented. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

The parameters to be analyzed are as follows:

- Hematology: red blood cell, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, white blood cells (WBC), and WBC differential (% and absolute) in neutrophils, eosinophils, basophils, lymphocytes, monocytes.

- Serum chemistry: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, cholesterol, uric acid, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, alkaline phosphatase, creatinine kinase, gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH).

- Urinalysis: specific gravity, pH, P/C ratio, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase, nitrate, microscopic examination, albumin/ creatinine ratio

- Coagulation: aPTT, PT, INR.

- Complement: C5a, Bb, C3.

- Biomarkers: C-reactive protein

Shift tables will be constructed for laboratory parameters to tabulate changes in DAIDS, Version 2.0, November 2014 from baseline to post-baseline worst DAIDS grade. Parameters to be tabulated will include:

- Hematology: absolute leukocyte count (ALC), absolute neutrophil count (ANC), hemoglobin, platelets, WBC
- Serum chemistry: Albumin, ALT, alkaline phosphatase, AST, bicarbonate, total bilirubin, direct bilirubin, calcium, creatinine, glucose, magnesium, sodium, potassium, uric acid

The mean and median estimates over time will be graphed for a selected list of lab parameters, including ALT, alkaline phosphatase, AST, serum creatinine, total bilirubin, LDH, and GGT from serum chemistry, hemoglobin, WBC, absolute neutrophil count, and platelets from hematology, C-reactive protein from biomarkers and aPTT from coagulation. The individual values over time will be graphed for above selected serum chemistry parameters, hematology and C-reactive as well. For mean/median/individual values figures over time, only the scheduled time points are included. By-patient listings to be presented include all lab tests.

### 9.3. Vital Sign Measurements

The actual values of vital sign parameters including oral temperature, heart rate, systolic and diastolic blood pressure, respiratory rate, and weight, will be summarized over time for each treatment group. Change from baseline will also be presented. The number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group. A by-patient listing will also be presented for all randomized patients.

### 9.4. Physical Examination

Physical examination results for all randomized patients will be presented in a listing.

### 9.5. Electrocardiogram

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time points. The number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

The ECGs will be listed in a by-patient listing for all randomized patients.

### 9.6. Study Drug (ISIS 505358 or Placebo) Stopping Rules

Patients meeting the following protocol-defined stopping criteria will be reported in the eCRF and presented in a by-patient listing.

### 9.6.1. Stopping Rules for Liver Chemistry Elevations

**Table 1 Study Drug Stopping Rules for ALT or AST Elevations**

| Baseline ALT ⩽ 2x ULN | Baseline ALT > 2 x ULN |
|---|---|
| If confirmed ALT or AST ⩾ 8 x ULN, permanently discontinue Study Drug | If confirmed ALT or AST ≥ 4 x Baseline, or confirmed ALT or AST ≥ 20 x ULN permanently discontinue Study Drug |
| If confirmed ALT or AST ≥ 3 to < 8 x ULN, permanently discontinue Study Drug if any of the following apply:<br>• appearance or worsening of symptoms felt by the Investigator to be potentially related to worsening of hepatic inflammation such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)<br>• total bilirubin > 1.5 x ULN and direct bilirubin > 35% | If confirmed ALT or AST ≥ 2 to < 4 x baseline, permanently discontinue Study Drug if any of the following apply:<br>• appearance or worsening of symptoms felt by the Investigator to be potentially related to worsening of hepatic inflammation such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)<br>• total bilirubin > 1.5 x ULN and direct bilirubin > 35% |

Note: Baseline is latest laboratory result prior to first dose of Study Drug (ISIS 505358 or placebo)
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of the laboratory reference range.
Refer to protocol Section 8.6.1 Table 3

### 9.6.2. Stopping Rules for Hematologic Test Results

1. Hemoglobin < 9.0 g/dL (i.e., ⩾ DAIDS Grade 3)
2. White Blood Cell count < 1.5 k/mm$^3$ (i.e., ⩾ DAIDS Grade 3)
3. Absolute neutrophil count < 0.75 k/mm$^3$ (i.e., ⩾ DAIDS Grade 3)
4. Platelet count < 75 k/mm$^3$

### 9.6.3. Stopping Rules for Renal Function Test Results

1. Confirmed serum creatinine increase that is both ≥ 0.3 mg/dL and ≥ 40% above Baseline creatinine values (defined as the average of the Screening and Study Day 1 results) and above upper limit of the reference range (i.e., > upper limit of the laboratory reference range [ULN])
2. Confirmed urine protein/creatinine ratio ≥ 0.90
3. Evidence of glomerular injury on urine microscopic exam.

### 9.6.4. Stopping Rules for Renal Function Test Results

In the event of clinical symptoms (e.g., constellation of symptoms such as severe fever, chills, and myalgia) or confirmed laboratory findings (e.g., substantial decrease in serum complement protein levels) consistent with a significant inflammatory reaction, and the event is without a probable cause other than Study Drug as discussed with the Ionis Medical Monitor, or designee, dosing of the patient with Study Drug will be stopped permanently.

### 9.7. Other Safety Data

Pregnancy testing result will be presented in a by-patient listing.

## 10. Pharmacokinetics

### 10.1. Pharmacokinetic Sample Concentrations

Study Drug (ISIS 505358) will be administered twice in Weeks 1 and 2 (on Days 1, 4, 8, and 11) and administered once weekly during Weeks 3 and 4 (i.e., on Days 15 and 22). Blood samples will be collected from each patient in all treatment groups according to the following schedule to allow for the determination of the PK of ISIS 505358.

Day 1: Pre-dose (prior to administration of ISIS 505358), 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours post SC injection

Day 2: 24 hour

Days 4, 8, and 15: Pre-dose

Day 22: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours post SC injection

Day 23: 24 hour

Days 29, 36, 57, 85, 113, and 211: Anytime

For Cohorts 1-3, blood samples collected on Days 29, 36, 57, 85, 113, and 211 will also be used to determine the concentration of nucleos(t)ide analogues (tenofovir and entecavir, if administered). For Cohort 4, blood samples collected at predose for Days 1, 8, 15, and 22 and on Days 29, 36, 57, 85, 113 and 221 will also be used to determine the concentration of nucleos(t)ide analogues. Plasma samples will be analyzed to determine the concentrations of ISIS 505358, tenofovir, and entecavir using validated bioanalytical methods.

Individual plasma concentrations and time deviation data will be presented in a data listing. For ease of presentation, plasma concentration data will be summarized by time-

point using the following descriptive statistics: sample size (n), arithmetic mean, standard deviation (SD), median, geometric mean, coefficient of variation (CV), interquartile range ($25^{th}$ percentile, $75^{th}$ percentile), minimum, and maximum. All plasma concentration values below the limit of quantification (BLQ) will be set to zero when calculating summary statistics. The individual, mean, and median plasma ISIS 505358, tenofovir, and entecavir concentration versus time profiles will be presented in figures on both linear and semi-logarithmic scales. Mean plasma concentration versus time profiles will be presented using nominal time and individual plasma concentration versus time profiles will be presented using actual time.

### 10.2. Pharmacokinetic Parameters

The individual plasma concentration versus actual time data for ISIS 505358 will be used to derive the following PK parameters using non-compartmental analysis, using Phoenix® WinNonlin® (Pharsight Corp, St. Louis, Missouri) Version 8.0 or higher.

| Parameter | Definition |
|---|---|
| $C_{max}$ | Observed maximum measured plasma concentration |
| $T_{max}$ | Time of observed maximum measured plasma concentration |
| $AUC_{0\text{-}24hr}$ | Area under the plasma-concentration time curve from time 0 to24 hours, calculated using the linear trapezoidal rule (calculated for Day 1 and Day 22) |
| $AUC_{\tau}$ | Area under the plasma-concentration time curve over a dosing interval, calculated using the linear trapezoidal rule (calculated for Day 22 only) |
| $t_{1/2\ \lambda z}$ | Apparent first-order terminal elimination half-life, calculated as $t_{1/2} = \ln 2/ \lambda z$ (Day 22 only) |
| $\lambda_z$ | Elimination rate constant estimated from the linear regression of the natural log-transformed concentration over time at the terminal phase (Day 22 only) |

For the calculation of PK parameters all plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. If 2 or more consecutive BLQ concentrations are followed by quantifiable concentrations, these quantified values will be set to missing. The BLQ values following the last quantifiable time-points will be set to missing. No concentration estimates will be imputed for missing sample values. Any sample with a missing value will be treated as if the sample had not been scheduled for collection and will be ignored when calculating mean concentrations or PK parameters.

Actual sampling times, rather than scheduled sampling times, will be used in the computation of PK parameters. The individual PK parameters of ISIS 505358 will be presented in a data listing. The PK parameters will be summarized using the following

descriptive statistics: n, arithmetic mean, SD, median, geometric mean (AUCs and $C_{max}$ only), CV, interquartile range ($25^{th}$ percentile, $75^{th}$ percentile), minimum, and maximum.

### 10.3. Dose Proportionality

Dose proportionality for ISIS 505358 will be performed using the power model, which can also be written in the linear relationship as:

$$\ln(\text{parameter}) = a + b*\ln(\text{dose})$$

where a value of b close to 1 indicates dose proportionality. The estimate of the intercept (a) and slope (b), their standard error and the 90% confidence interval (CI) will be obtained from the model. Parameters include $AUC_{0\text{-}24hr}$, $AUC_{\tau}$, and $C_{max}$ from Day 1 and Day 22.

Dose proportionality is concluded when the 90% CIs of the slope b lie entirely within (1 + ln(0.8)/ln(r), 1 + ln(1.25)/ln(r)) where r is a ratio that describes the dose range and is defined as (highest dose/lowest dose) (2.219, 3.330) (Smith et al, 2000).

To explore the effect of prior ISIS 505358 exposure on the plasma concentrations of tenofovir (and entecavir) administered after the conclusion of ISIS 505358 administration, the plasma concentrations of tenofovir (and entecavir) between different treatments (150 mg ISIS 505358, 300 mg ISIS 505358, 450 mg ISIS 505358 and placebo) will be compared using a repeated-measures analysis of variance (ANOVA). The analysis will be performed on original scale (untransformed) and natural log (ln) transformed plasma concentrations of tenofovir (and entecavir). The model will include fixed effects for treatments (150 mg ISIS 505358, 300 mg ISIS 505358, 450 mg ISIS 505358 and placebo) and day (Days 36, 57, 85, 113, and 211), along with day-by-treatment interaction. Day will be specified as a repeated variable for each patient. Each ANOVA will include calculation of treatment and day-by-treatment interaction least-squares (LS) means, the difference between LS means, corresponding 90% confidence interval. The concentration used in all analyses will be tested for normality. If the data does not appear to be normally distributed, a nonparametric analysis will be used on the untransformed data. Statistical analysis will be performed using PROC MIXED.

Only descriptive statistics will be reported for Cohort 4.

## 11. Interim Analysis

There is no formal interim analysis planned.

PPD Biostatistics and Programming team will remain blinded during the entire treatment period.

An unblinded interim analysis for Cohorts 1-3 may be performed after all Cohorts 1-3 patients have progressed beyond their Study Day 29 assessments and the databased has been locked. An unblinded interim analysis for Cohort 4 may be performed similarly after all Cohort 4 patients have progressed beyond their Study Day 29 assessments and locking of the data.

If the unblinded interim analysis is recommended by the DSMB, the PPD Biostatistics and Programming team will be unblinded and then produce a subset of the full analysis TLFs for the interim review.

## 12. Changes in the Planned Analysis

There is no change made to the planned analyses from the protocol.

Reference materials for this statistical analysis plan include Clinical Study Protocol ISIS 505358-CS3 Amendment 2 - Korea (22 November 2016) and ISIS 505358 Hepatitis B Virus Antisense Oligonucleotide Investigator's Brochure Revision 3 (23 February 2016).

## 13. References

Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000;17(10):1278-83.

## 14. Appendices

### 14.1. Schedule of Study Procedures – Cohorts 1-3

| | Screen | Treatment (4 wks) | | | | | | | | Post-Treatment Follow-Up (26 wks) | | | | | | Early Term |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week (W) and/or Study Day** | **S-28 to S-1** | **W1 D1** | **W1 D2** | **W1 D4** | **W2 D8** | **W2 D11** | **W3 D15** | **W4 D22** | **W4 D23** | **W5 D29** | **W6 D36** | **W9 D57** | **W13 D85** | **W17 D113** | **W31 D211** | |
| **Allowed Variance Window *** | **n/a** | **n/a** | **^** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **^** | **§** | **± 1** | **± 3** | **± 7** | **± 7** | **± 7** | **n/a** |
| Study Drug Administration | | X | | X | X | X | X | X | | | | | | | | |
| Tenofovir (or entecavir) Daily Administration | | | | | | | | | | X [e] | X | X | X | X | X | |
| Informed Consent | X | | | | | | | | | | | | | | | |
| Inclusion/Exclusion, Medical History | X | | | | | | | | | | | | | | | |
| Body Weight and Height [1] | X | X [a] | | | | | | X | | X [a] | | X | | X | X | X |
| Physical Exam | X | | | | | | | | | X [a] | | | | X | X | X |
| Vital Signs[2] | X | X [a] | X | | X [a] | X [a] | X [a] | X [a] | X | X [a] | X | X | X | X | X | X |
| HIV, Hepatitis C & D | X | | | | | | | | | | | | | | | |
| Pregnancy Test [3] | X | X | | | | | | | X | | X | | X | X | X | X |
| Alpha-fetoprotein | X | | | | | | | | | | | | | | | |
| Chemistry, Hematology, Urinalysis [5] | X | X [a] | X [b] | | X [a] | | X [a] | | X [b] | X [a] | X | X | X | X | X | X |
| Complement C3 | X | X [a] | | | X [a] | | X [a] | X [a] | | X [a] | X | X | | X | X | X |
| Complement split products | | X [c] | X [b] | | | | | X [c] | X [b] | | X | X | | X | X | X |
| PT, INR, aPTT | X | X [a] | X [b] | | | | | X [c] | X [b] | | X | X | | X | X | X |
| C-reactive protein | X | X [a] | X [b] | X [a] | X [a] | | X [a] | X [a] | X [b] | X [a] | X | X | | X | X | X |
| Quantitative HBsAg, HBeAg, HBV DNA | X | X [a] | | | | | X [a] | | X | X [a] | X | X | X | X | X | X |
| Anti-HBs and anti-HBe antibodies | X | X [a] | | | | | | | | X [a] | | X | | X | X | X |
| HBsAg genotype | | X [a] | | | | | | | | | | | | | | |
| HBV Drug Binding Sites DNA Sequence | | X [a] | | | | | | | | X [a] | | | | X | | X |
| Archived Serum & Plasma Samples [6] | X | X [a] | X [b] | | X [a] | | X [a] | X [a] | X [b] | X [a] | X | X | X | X | X | X |
| Archived PBMC Samples[7] | | X [a] | | | | | X [a] | | | X [a] | | X | | X | X | X |
| ECG (12-Lead) in triplicate at each time point | X | X [c] | X [b] | | | | | X [c] | X [b] | X [a] | | | | X | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tenofovir (or entecavir) concentration [8] | | | | | | | | | | X [a] | X | X | X | X | X | X |
| ISIS 505358 PK Blood Sampling [9] | | X [d] | X [b] | X [a] | X [a] | | X [a] | X [d] | X [b] | X [a] | X | X | X | X | X | X |

## 14.2. Schedule of Study Procedures – Cohort 4

| | Screen | Treatment (4 wks) | | | | | | | | Post-Treatment Follow-Up (26 wks) | | | | | | Early Term |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Week (W) and/or Study Day** | **S-28 to S-1** | **W1 D1** | **W1 D2** | **W1 D4** | **W2 D8** | **W2 D11** | **W3 D15** | **W4 D22** | **W4 D23** | **W5 D29** | **W6 D36** | **W9 D57** | **W13 D85** | **W17 D113** | **W31 D211** | |
| **Allowed Variance Window *** | **n/a** | **n/a** | **^** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **^** | **§** | **± 1** | **± 3** | **± 7** | **± 7** | **± 7** | **n/a** |
| Study Drug Administration | | X | | X | X | X | X | X | | | | | | | | |
| Nucleos(t)ide Analogue Daily Administration | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Informed Consent | X | | | | | | | | | | | | | | | |
| Inclusion/Exclusion, Medical History | X | | | | | | | | | | | | | | | |
| Body Weight and Height [1] | X | X [a] | | | | | | X | | X [a] | | X | | X | X | X |
| Physical Exam | X | | | | | | | | | X [a] | | | | X | X | X |
| Vital Signs[2] | X | X [a] | X | | X [a] | X [a] | X [a] | X [a] | X | X [a] | X | X | X | X | X | X |
| HIV, Hepatitis C & D | X | | | | | | | | | | | | | | | |
| Pregnancy Test [3] | X | X | | | | | | | X | | X | | X | X | X | X |
| Alpha-fetoprotein | X | | | | | | | | | | | | | | | |
| Chemistry, Hematology, Urinalysis [5] | X | X [a] | X [b] | | X [a] | | X [a] | | X [b] | X [a] | X | X | X | X | X | X |
| Complement C3 | X | X [a] | | | X [a] | | X [a] | X [a] | | X [a] | X | X | | X | X | X |
| Complement split products | | X [c] | X [b] | | | | | X [c] | X [b] | | X | X | | X | X | X |
| PT, INR, aPTT | X | X [a] | X [b] | | | | | X [c] | X [b] | | X | X | | X | X | X |
| C-reactive protein | X | X [a] | X [b] | X [a] | X [a] | | X [a] | X [a] | X [b] | X [a] | X | X | | X | X | X |
| Quantitative HBsAg, HBeAg, HBV DNA | X | X [a] | | | | | X [a] | | X | X [a] | X | X | X | X | X | X |
| Anti-HBs and anti-HBe antibodies | X | X [a] | | | | | | | | X [a] | | X | | X | X | X |
| HBsAg genotype | | X [a] | | | | | | | | | | | | | | |
| HBV Drug Binding Sites DNA Sequence | | X [a] | | | | | | | | X [a] | | | | X | | X |
| Archived Serum & Plasma Samples [6] | X | X [a] | X [b] | | X [a] | | X [a] | X [a] | X [b] | X [a] | X | X | X | X | X | X |
| Archived PBMC Samples[7] | | X [a] | | | | | X [a] | | | X [a] | | X | | X | X | X |
| ECG (12-Lead) in triplicate at each time point | X | X [c] | X [b] | | | | | X [c] | X [b] | X [a] | | | | X | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Nucleos(t)ide Analogue concentration[8] | X[10] | X | | | X | | X | X | | X [a] | X | X | X | X | X | X |
| ISIS 505358 PK Blood Sampling [9] | | X [d] | X [b] | X [a] | X [a] | | X [a] | X [d] | X [b] | X [a] | X | X | X | X | X | X |

* A window of ± 1 day is allowed for the Study Day 4–22 visits. However, the administration of Study Drug doses should be separated by at least 36 hours. Following a variance, the patient should return to the schedule based on elapsed days from the actual Day 1 (i.e., variances do not permanently shift the schedule).
^ Day 2 and Day 23 visits must occur on the day after the actual Day 1 and Day 22 visits, respectively
§ Every attempt should be made for the Study Day 29 visit to occur 7 days after the actual occurrence of Study Day 22
n/a Not applicable

Note: If not specifically labeled, "X" means anytime

1 Height measured at Screen visit only
2 BP, HR, RR, temp
3 Women who are not surgically sterile or post-menopausal
4 Women who are post-menopausal and not surgically sterile
5 If hematuria or 2 + proteinuria is observed, see confirmation guidance in protocol Section 8.5
6 Stored at -80° C for retrospective clinical safety, immunologic, and/or virologic assays (e.g., retrospective LDH or CPK isoform measurements, measurement of cytokine and/or chemokine levels, and/or measurement of additional markers of kidney function, or mutation analysis of breakthrough HBV) in this or subsequent clinical studies of ISIS 505358
7 PBMC samples prepared from whole blood, frozen and stored for analysis at future time to be determined based upon results from HBV tests
8 Time of nucleos(t)ide administration and fed/fasted status at time of dose ingestion must be recorded. Time and fed/fasted status does not need to be controlled, but should be similar on each blood draw day
9 See also protocol Appendix C
10 Measurement result not required for Screen pass/fail decision

Time (time is in reference to Study Drug administration):
a Pre-dose (for Day 29, is before first nucleos(t)ide analogue dose)
b 24-hour
c Pre-dose and 3 and 5 hours post-dose
d 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours post-dose
e Initiate dosing after specimen collections for Day 29 laboratory tests

## 15. Table of Contents: Tables, Listings and Figures

Note:
Per Protocol Amendment #3, Cohort 4 has been introduced to this study. Outputs are doubled for subjects in Cohort 4.

- Appendix of "- Cohorts 1 to 3" will be added into title of all outputs for subjects in these Cohorts;
- Appendix of "- Cohort 4" will be added into Titles of all outputs for subjects in Cohort 4, and appendix of "a" will be added to their Table Numbers;
- Table 14.2.1.5a, Table 14.2.1.6a, and Table 14.2.1.7a were not produced due to small sample size of Cohort 4.

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Date: 18 December 2019

To: Memo To File

From: PPD , Biostatistics Team Leader

Re: Ionis Pharmaceuticals, ISIS 505358-CS3

Explanation of changes and Add-on to full analysis package

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(1) Typographical errors of statistical analysis plan version 3.0 and table shell need to be corrected as below. The results of vital sign measurement and electrocardiogram need not to be summarized for patients who experience abnormalities in clinical laboratory evaluations because the datasets cannot be directly linked and are generally summarized separately.

- Remove 'The number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.' from section 9.3 and 9.5, and remove table 14.4.5.3 and 14.4.6.3 from section 15 of statistical analysis plan version 3.0.
- Remove table 14.4.5.3, 14.4.6.3, 14.4.5.3a, and 14.4.6.3a from table shell.

(2) Upon receiving the request to know that ad-hoc TLF package should be added to the final CSR packages, this memo to file is created to document that TLFs specified in full analysis shells and ad-hoc shells will both be included in full analysis package.

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PPD

PPD

Date

Manager or Senior Review Signature (optional) Date

***NOTE:*** *It is preferable that the reviewing management team member provides a secondary signature on MTFs to ensure that the wording accurately describes the intention of the issue being addressed. If this secondary signature is not implemented, the optional management signature line should be removed from the MTF template during generation.*