Efficacy and Safety of ACC007 in Combination with 3TC+TDF for HIV/AIDS

Phase III clinical trial protocol

Clinical Approval Number	2017L01340
Program Number	ADYY- ACC007-301
Duration of Clinical Trials	September 2018～September 2021
Sponsor	Jiangsu Aidea Pharmaceutical Co., Ltd.
Project Leader	Shen Xiaoning
Phone	025-85578729
Group Leader Agency	Beijing Youan Hospital, Capital Medical University
Principal Investigator	Wu Hao
Phone	010-83997962
Participating Agencies	Beijing Ditan Hospital, Capital Medical University; Guangzhou Eighth People's Hospital, Guangzhou Medical University; Infectious Disease Hospital of Henan Province; the First Hospital of Changsha; Chongqing Public Health Medical Center; The Second Hospital of Nanjing
Pharmacogenetic Analysis and Testing Agency	Chinese Academy of Sciences Shanghai Institute of Materia Medica
Project Leader	Chen Xiaoyan
Phone	021-50800738
Data Management Agency	Beijing Zhiji Pharmaceutical Information Consulting Co., Ltd.
Project Leader	Zhang Ting
Phone	010-58648971
Statistical Analysis Agency	Beijing Bozhiyin Technology Co., Ltd.
Project Leader	Zheng Qingshan
Phone	010-67587407
Clinical Trial Monitoring Agency	Beijing Co-CRO Medical Development Co., Ltd.
Project Leader	Peng Haiyan
Phone	010-85116590

Program Summary

<table>
<tr><td>Research Title</td><td>Phase III clinical study of the efficacy and safety of ACC007 in combination with 3TC+TDF in the treatment of HIV/AIDS</td></tr>
<tr><td>Clinical Research Agency</td><td>Group leader: Beijing Youan Hospital, Capital Medical University
Participating agencies: Beijing Ditan Hospital, Capital Medical University
Guangzhou Eighth People's Hospital, Guangzhou Medical University
Infectious Disease Hospital of Henan Province
The First Hospital of Changsha
Chongqing Public Health Medical Center
The Second Hospital of Nanjing</td></tr>
<tr><td>Objectives of the Study</td><td>Primary Objective
■ Demonstrate that the proportion of subjects with virological response (VL < 50 copies/mL) in the ACC007 group is not inferior to the EFV control group at 48 weeks of treatment for HIV/AIDS without ARV, with a non-inferiority threshold of 10%
Secondary Objective
■ To evaluate and compare antiviral activity (HIV-RNA levels) between the ACC007 and EFV groups at 48 weeks
■ To evaluate and compare the safety of the ACC007 and EFV groups at 48 weeks
■ To evaluate and compare the changes in immune function (CD4 cell counts) between the ACC007 and EFV groups at 48 weeks
■ To evaluate the population pharmacokinetic (popPK) characteristics of ACC007 and PK/PD (PK/HIV RNA vs. PK/AE) relationship
■ To evaluate the safety at 24 weeks of treatment
■ To evaluate the proportion of subjects with virological response (VL < 50 copies/mL at 96 weeks of treatment
■ To evaluate antiviral activity (HIV RNA levels) at 96 weeks of treatment
■ To evaluate the safety at 96 weeks of treatment
■ To evaluate the changes in immune function at 96 weeks of treatment (CD4 cell counts)</td></tr>
<tr><td>Study Design</td><td>Multicenter, randomized, double-blind, double-simulation, positive parallel-controlled, non-inferiority phase III clinical trial</td></tr>
<tr><td>Subgroups and Sample Size*</td><td>
<table>
<tr><th>Group</th><th>Experimental drugs</th><th>Sample size (Number)</th><th>Treatment period (Blind state/week)</th><th>Extension period** (Open/week)</th></tr>
<tr><td>Test group</td><td>ACC007 150 mg + EFV placebo + (3TC 300mg+TDF 300mg)</td><td>315</td><td>48</td><td rowspan="2">48</td></tr>
<tr><td>Control group</td><td>EFV 600mg +ACC007 placebo + (3TC 300mg+TDF 300mg)</td><td>315</td><td>48</td></tr>
</table>
*Non-inferiority design: with an efficiency of 80%, α=0.025, β=0.2, δ=0.10, ratio=1:1, and the estimated shedding rate=20%.
**At the end of the 48-week study up to week 96, all subjects are no longer taking the placebo and may choose to enter the extension study, continue treatment with ACC007+3TC+ TDF or EFV+3TC+ TDF, or be coordinated for transfer to the National Free Treatment System, depending on the subject's preference.</td></tr>
<tr><td>Inclusion and Exclusion Criteria</td><td>Selection Criteria
(1) 18-65 years old
(2) Diagnosed with HIV-1 infection, HIV RNA ≥ 1000 copies/mL within 30 days before enrollment and subject is judged to be suitable for ART regimen by the investigator
(3) Never received ARV treatment or therapeutic HIV-1vaccine and agree not to initiate ART treatment</td></tr>
</table>

	before the baseline visit (4) Understand and comply with the requirements of the study protocol and voluntarily sign a written informed consent form **Exclusion Criteria** (1) Status of acute HIV-1 infection or currently suffering from AIDS related complex (2) History of drug abuse, recent history of alcohol or drug dependence (3) Any condition considered by the investigator that may compromise the safety of the subject and affect compliance with the study protocol (4) Participated in a clinical trial with an investigational compound/therapeutic device within 30 days prior to enrollment in this study (5) Used systemic immunosuppressive therapy or immunomodulators within 30 days prior to treatment in this study, or could not avoid to use during the clinical trial (6) Hepatitis C or hepatitis B with glutathione > 4 times ULN (7) [1] Creatinine ≥ ULN and a glomerular filtration rate (GFR) ≤ 60 (mL/minute/1.73 m^2) as derived from the $CKD\text{-}EPI_{creatinine}$ formula (GFR = a*(serum creatinine)/b)^c*(0.993)^age. The a values are differ according to gender and ethnicity: blacks: females = 166, males = 163; whites and other ethnicities: females = 144, males = 141. The b values differ according to sex: females = 0.7; males = 0.9. The c values differ according to sex and serum creatinine values: females: c = -0.329 for serum creatinine ≤ 0.7 mg/dL, c = -1.209 for serum creatinine > 0.7 mg/dL; males: c = -0.411 for serum creatinine ≤ 0.7 mg/dL, c = -0.411 for serum creatinine > 0.7 mg/dL. (c=-1.209 for serum creatinine > 0.7 mg/dL.) (8) Grade 3 or 4 presentation according to the DAIDS grading scale[2] (9) Active pulmonary tuberculosis and is on treatment at the time of screening (subjects who develop active pulmonary tuberculosis during the trial will be withdrawn from treatment in order to start anti-tuberculosis therapy) (10) Received antifungals, corticosteroids, and sulfonamides and antituberculosis drugs within 14 days prior to study screening or is taking these drug. (11) A history of allergy or hypersensitivity to any component or excipient of the investigational drug (12) Women who are pregnant or breastfeeding; women of childbearing potential who are not using contraception (e.g., diaphragm; condom; IUD, etc.; partner vasectomy) deemed effective by the investigator; female subjects who are unwilling to continue using an investigator-approved form of contraception from screening until 6 months after the last dose of trial drug. Male subjects with active heterosexual sex without vasectomy who are not using birth control, or who do not wish to continue using contraception during the trial until at least within 30 days after the end of the trial.
Study Procedures	● Visits: Screening, baseline, 4w, 12w, 24w, 36w, 48w, 72w, 96w visits respectively, during which the study components such as consultation, physical examination, specimen collection and/or drug retrieval and distribution required for efficacy and safety assessment will be completed according to the protocol requirements ● Population pharmacokinetic study: 1 PK blood sample will be collected on an empty stomach at the 12w, 24w, 36w and 48w visits and combined with the pre-dense sampling data for population pharmacokinetic analysis. ● PK-collected blood samples will be tested for both blood drug concentrations and HIV RNA levels
Experimental Drugs	● ACC007: 75 mg/tablet, 2 tablets each time, once-daily (at night before bedtime) ● ACC007 placebo: 2 tablets each time, once-daily (at night before bedtime) ● Efavirenz: 600mg/tablet, 1 tablet each time, once-daily (take at night before bedtime) ● Efavirenz placebo: 1 tablet each time, once-daily (at night before bedtime)

	● Lamivudine: 300 mg/tablet, 1 tablet each time, once-daily (at night before bedtime) ● Tenofovir: 300 mg/tablet, 1 tablet each time, once-daily (at night before bedtime) If you are found to have missed a dose of medication, you are required to take one dose before 12:00 noon the following day; no dose will be taken after 12:00 noon.
Efficacy Assessment	**Primary endpoint indicators.** ● Percentage of subjects with HIV RNA <50 copies/mL at 48 weeks of treatment (RT-PCR Abbott). Evaluation using Snapshot Approach method[3] **Secondary endpoint indicators** ● Changes in HIV RNA log values at 48 and 96 weeks of treatment ● Percentage of HIV RNA levels ≤400 copies/mL at 48 and 96 weeks of treatment ● Percentage of subjects with HIV RNA levels <50 copies/mL at 96 weeks of treatment ● Changes in CD4 cell counts at 48 and 96 weeks of treatment
Safety Assessment	**Clinical Safety Assessment** ● Subjects' spontaneous reports or direct physician observation or non-induced questioning of subjects about adverse events will be collected during the clinical trial and evaluated at 24, 48 and 96 weeks of treatment. **Laboratory Safety Assessment** ● The changes of routine blood test, routine urine test, blood biochemistry and electrocardiogram at 24, 48 and 96 weeks will be compared, and urine pregnancy test (only for women of childbearing age), abdominal ultrasound and chest X-ray will be performed during the clinical trial to evaluate their safety.
PK/PD Assessment	Blood sample specimens of ACC007 will be obtained by sparse sampling, and the relationship between blood concentration and HIV RNA level and AE incidence will be measured, and the relationship between PK/HIV RNA and PK/AE will be analyzed using modeling.(Preparing for independent publication)
Medication Adherence Assessment	**Medication adherence assessment (%)** = Actual number of medications / Theoretical number of medications × 100% **Adherence assessment:** ACC007 or efavirenz with (3TC+TDF) calculated separately. This study required medication adherence of ≥90% and ≤110%.
Statistical Analysis	● SAS 9.4 software will be used for analysis. Non-inferiority tests will be expressed using two-sided 95% confidence intervals for the differences between groups ● The general statistical tests are two-sided tests, and a p-value less than or equal to 0.05 will be considered statistically significant

Abbreviations

Symbols	Definition	Symbols	Definition
3TC	Lamivudine	IC_{50}	Semi-inhibitory concentration
ABC	Abacavir	IEC	Ethics Committee
AE	Adverse Events	KET	Urine ketone bodies
ALB	Albumin	LDH	Lactate dehydrogenase
ALP	Alkaline phosphatase	LEU	Urine leukocytes
ALT	Alanine aminotransferase	MCH	Mean red blood cell hemoglobin content
APTT	Partial thromboplastin time	MCHC	Mean red blood cell hemoglobin concentration
ART	Anti-retroviral therapy	MCV	Mean erythrocyte product
AST	Aspartate aminotransferase	NOEL	Maximum no effect dose
$AUC_{(0-\infty)}$	Area under the blood drug concentration-time curve from zero to infinity time	NOAEL	Visible adverse effect dose
$AUC_{(0-t)}$	Area under the blood concentration-time curve from zero to the last measurable concentration	NVP	Nevirapine
AZT	Zidovudine	PLT	Platelet count
BIL	Urine bilirubin	PopPK(PPK)	Population pharmacokinetics
BUN	Urea nitrogen	PPS	Compliant with the program set
BLD	(urinary) red blood cells	PRO	Urine protein
CHOL	Cholesterol	RBC	Red blood cell count
CK	Creatine kinase	RAL	Raltegravir
C_{max}	Drug peak concentration	SAE	Serious Adverse Events
CREA(CR)	Blood creatinine	SG	Urine specific gravity
CRF	Case report form	SS	Secure data sets
C_{trough}	Valley concentration	$T_{1/2}$	Half-life
DBIL	Direct bilirubin	TBIL	Total bilirubin
ECG	Electrocardiogram	TDF	Tenofovir
EDC	Electronic Data Management	TG	Triglyceride
FTC	Emtricitabine	T_{max}	Peak time
GCP	Quality management standard for drug clinical trials	TP	Total protein
γ-GT	Glutamyl aminotransferase	UBG	Urobilinogen
GLU	Blood/urine glucose	UPh	Urine Ph
HBV-M	Hepatitis B two-for-half	UREA	Urea
HCT	Erythrocyte specific gravity	UBG	Urobilinogen
HGB	Hemoglobin	WBC	Leukocyte count
Anti-HCV	Hepatitis C antibody		

Flow Chart

Research Phase	Screening Period	Baseline Period	Treatment Period (blind state period)					Extension Period (open period)	
Visits (times)	1	2	3	4	5	6	7	8	9
Time period/point	**-30d～-1d**	**-7d～1d**	**4w±3d**	**12w±4d**	**24w±6d**	**36w±6d**	**48w±6d**	**72w±12d**	**96w±12d**
Sign the Informed Consent Form	x								
Inclusion/Exclusion Criteria	x	x							
Demographic Information	x								
Medical History	x								
HIV Confirmation	x								
Medication Adherence Education and Assessment	x	x	x	x	x	x	x	x	x
Random		x							
Physical Examination	x	x	x	x	x	x	x	x	x
Vital Signs Measurement	x	x	x	x	x	x	x	x	x
Routine Blood Test	x[6]	x[7]	x	x	x	x	x	x	x
Routine Urine Test	x[6]	x[7]	x	x	x	x	x	x	x
Urine Pregnancy Test (women of childbearing age)		x		x	x	x	x	x	x
Blood Biochemistry[1]	x[6]	x[7]	x	x	x	x	x	x	x
CD4 Cell Count	x[6]	x	x	x	x	x	x	x	x
HIV RNA[2] (tested at each center)	x[6]			x	x				
HIV RNA[3] (specimen collection)		x	x	x	x	x	x	x	x
Collect Plasma for Drug Resistance Test[4]		x			x		x		x
Collect Plasma for PPK[5]				x	x	x	x		
Hepatitis B Screen	x[6]								
Hepatitis C Antibody	x[6]								
RPR Titer	x[6]								
Urine Drug Test Screening	x								
12-lead Electrocardiogram	x[6]	x[7]	x	x	x	x	x	x	x
Ultrasound of the Abdomen	x[6]						x		x
Chest X-Ray	x[6]						x		x
Combining Medication Records	x	x	x	x	x	x	x	x	x
Adverse Event Record			x	x	x	x	x	x	x
Drug Distribution		x	x	x	x	x	x	x	
Drug Recall			x	x	x	x	x	x	x
Test Summary							x		x

1. Tests include ALT, AST, GGT, ALP, LDH, CK, AMY, TBIL, DBIL, GLU, UA, BUN, CREA, CHOL, TG, TP, ALB.

2. HIV RNA primary screening (inclusion criteria), 12 weeks, and 24 weeks (determination of virological failure) were performed once at each study center.

3. For subjects who met the enrollment criteria, plasma specimens were retained by each center at baseline and at each subsequent visit for HIV RNA, and sent to the central laboratory for uniform testing.

4. Retain the specimens and send them to the central laboratory for uniform testing if necessary.

5. PPK specimens were collected at 12, 24, 36 and 48 weeks visits on an empty stomach and the time of PPK collection was recorded, along with the time of last meal and last dose. PPK blood samples were to be tested uniformly in the central laboratory (only blood samples from the treatment group were tested).

6. Subjects' test results within 30 days prior to screening at our study center can be used directly (including routine blood, urine, blood biochemistry, CD4 cell count, HIV RNA, hepatitis B markers, hepatitis C antibodies, RPR titer, 12-lead ECG, abdominal ultrasound, and chest X-ray).

7. Baseline ≤7 days from the screening period may not be repeated (including routine blood, urine, blood biochemistry, 12-lead ECG.

Table of Contents

List of Tables

List of Figures

Text of the Clinical Study Protocol

1 Background

The morbidity and mortality of HIV-1-infected patients were significantly reduced after the application of highly active antiretroviral therapy to control and prevent HIV replication[1]. Antiretroviral drugs act on three intra-viral enzymes (reverse transcriptase, protease, and integrase), viral envelope glycoproteins, host cell proteins, and CCR5 chemokine co-receptors. According to their mechanism of action, there are six different anti-HIV drugs: nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), fusion inhibitors (FI), integrase strand transfer inhibitors (INSTI) and co-receptor inhibitors (CI). The appropriate combination of these drugs can effectively suppress HIV infection. The principle of combination drug use is dependent on the therapeutic efficacy of the combined regimen, the efficacy of the drug used by other patients, potential adverse drug reactions, and patient's adherence to the given regimens[2] .

The HIV Pol gene encodes three enzymes (with four enzymatic activities): protease, reverse transcriptase (with embedded RNAseH), and integrase. HIV replication requires these four enzymes, including protease, reverse transcriptase, RNAseH, and integrase. Among them, the reverse transcriptase is an asymmetric heterodimer containing the p66 and p51 subunits, both of which are encoded by the same gene sequence in the viral genome, and p51 subunit is obtained by cleaving the p66 subunit by viral protease. Both NRTI and NNRTI can inhibit reverse transcriptase.

Although the chemical composition of the NNRTI class is different, all NNRTIs react with the hydrophobic region near the active center of reverse transcriptase to alter the structure of reverse transcriptase and thereby inhibit its activity. NNRTI in combination with nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) constitute a highly effective therapy for treatment naïve individuals living with HIV and have emerged as a treatment option.

Efavirenz (EFV) and nevirapine (NVP) are the two representative varieties of the NNRTI class, with efavirenz being the most prescribed drug. Currently, the most widely used first-line regimen for treatment-naïve patients in China is two NRTIs (TDF or AZT + 3TC) plus one NNRTI (EFV or NVP). Among the NNRTI drugs, NVP has a serious impact on medication adherence due to adverse effects such as rash and liver toxicity, and its clinical use is also limited by the need for introductory monitoring. EFV not only has a low genetic barrier that prone to mutation and drug resistance, but also has adverse effects on the central nervous system, and poor drug adherence is the main reason for the emergence of drug resistance mutations. In addition, EFV is teratogenic and contraindicated for certain populations. With the increasing use of EFV in first-line treatment regimens, many newly infected patients have been detected with

EFV-resistance, and these patients cannot be treated with the regimens containing EFV. Therefore, there is a significant clinical need to develop new NNRTI drugs that can effectively suppress EFV-resistant strains and have lower adverse effects, which can not only fight against major NNRTI-resistance mutations, but also improve safety and medication adherence.

ACC007 is a novel NNRTI for the treatment of HIV. [redacted] ACC007 is a new NNRTI with favorable safety and pharmacological properties found in preclinical studies, requiring only once-daily administration. ACC007 is less likely to have efavirenz-like CNS symptoms and has activity against the major efavirenz resistance mutation (K103N). Although its antiviral activity against laboratory-cultured strains and clinical isolates of HIV-1 is low, it shows activity in HIV-1 resistant to NRTI, PI, and INSTI, and combined with these types of drugs can increase the antiviral activity of ACC007. Moreover, compared to other NNRTIs, ACC007 showed lower plasma protein binding and its protein-adjusted antiviral activity was comparable to efavirenz.

The recommended initial treatment regimens in HIV antiretroviral treatment guidelines issued by the U.S. Department of Health and Human Services in 2014 include: NNRTIs-based regimens (2NRTIs + 1NNRTI), PIs-based regimens (2NRTIs + 1PI) and INSTIs-based regimens (2NRTIs + 1 INSTI) [3]. The "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection" issued by the World Health Organization (WHO) in 2013 recommended the first-line regimens of 2NRTIs + 1NNRTI[4]. Currently, the first-line ART regimens in China are two NRTIs (TDF or AZT+ 3TC) plus one NNRTI (EFV or NVP).

Based on the recommendations of domestic and international treatment guidelines and the long-term and extensive clinical evidence base of "2NRTIs + 1NNRTI", we propose to select ACC007 in combination with (3TC + TDF) for the subsequent anti-HIV clinical treatment. ACC007 is not yet on the market, so a drug interaction study of ACC007 in combination with 3TC+TDF is required first.

1.1 ACC007 Pharmacy Research

Product Name: ACC007

Chemical name: [redacted]

[redacted]

Chemical structure formula:

Molecular formula: [redacted]

Molecular weight: [redacted]

Physicochemical properties: This product is a crystalline solid, white to off-white powder.

Functions and indications: Non-nucleoside reverse transcriptase inhibitor, combined with other antiretroviral drugs for the treatment of HIV/AIDS.

Description of prescription: ACC007 from Jiangsu Aidea Pharmaceutical Co., Ltd. is the same as [redacted].

1.2 ACC007 Pharmacodynamic Studies

ACC007 showed antiviral activity (IC_{50}) of 5-7 nM against HIV-1 isolates from laboratory cell lines and human peripheral blood mononuclear cells. The average EC_{50} was 10.4 nM when tested against a group of 20 HIV-1 strains representing 10 different subtypes from multiple regions of the world. ACC007 showed no significant decrease in the activity of HIV-1 with NRTIs, PIs and INSTIs resistance mutations. And it had synergistic antiviral effects with TFV, FTC, 3TC, AZT, ABC, LPV, ATV, RAL and EVG. Compared to other NNRTIs, ACC007 showed lower human serum protein binding with a protein-adjusted EC_{50} of 23 nM, comparable to EFV (16 nM). ACC007 showed approximately 7 to 10-fold reduced activity against viral strains containing single RT mutations K103N, Y181C and G190A. In vitro resistance selectivity against two wild-type (WT) HIV-1 viral strains, HIV-1 IIIb and NL4-3, in MT-4 cells resulted in the emergence of viral libraries containing NNRTI binding site mutations K103N, Y181C, L214F, F227L and V106A, F227L, respectively. Both ACC007-selected mutant viral strains showed more than 70-fold reduced susceptibility to ACC007 and cross-resistance to EFV.

In binding assays using the MDS Pharma Lead Profiling Screen and Cerep safety profile screen with over 200 ion channels, receptors and enzymes, ACC007 did not bind significantly to any target at a concentration of 10 μM. While EFV inhibited ligand binding of many receptors present in the CNS in the Cerep screen. It can be seen that the drug off-target effect of ACC007 in the CNS may be relatively low compared to EFV.

In conclusion, results of several preclinical efficacy studies have shown that ACC007 has low nanomolar activity

against HIV-1 laboratory strains and clinical isolates in passaged cell lines and human peripheral blood mononuclear cells. ACC007 also has activity against HIV-1 containing NRTIs, PIs and INSTs resistance mutations, and ACC007 showed good synergistic effects in combination with these classes of drugs. These results suggest that ACC007 has good promise for the treatment of HIV/AIDS.

1.3 ACC007 Pharmacology Studies

Safety pharmacology studies were conducted to determine the potential cardiovascular, respiratory and central nervous system effects of ACC007. The IC_{50} prediction for ACC007 on the hERG potassium channel is greater than the upper solubility limit of 50 mM. Therefore, ACC007 may have a negligible risk of arrhythmia in humans due to QT interval prolongation.

The pharmacological effects of ACC007 on the central nervous system were assessed in male mice administered orally at single doses of 0, 100, 500 or 1500 mg/kg. No dosing-related effects were observed for any of the qualitative or quantitative parameters of the modified Irwin Screen assessment test. Based on these results, the NOEL for ACC007 in this study was determined to be 1500 mg/kg.

In a study assessing the pharmacological effects of ACC007 on respiratory, hemodynamic and ECG parameters by telemetry after oral administration in beagle dogs, no drug-related effects were found for all parameters at dose levels of 15, 50 and 150 mg/kg. Based on these results, the NOEL for ACC007 in this study was determined to be 150 mg/kg.

1.4 ACC007 Toxicology Studies

The potential acute toxicity of ACC007 was observed in mice by single oral gavage doses of 100, 500, and 1500 mg/kg/day for 14 days, and the study suggested a no-observed-adverse-effect dose level (NOAEL) of 1500 mg/kg/day for ACC007.

The potential toxicity and toxicokinetics of ACC007 were observed by oral gavage of mice at doses of 100, 500, and 1500 mg/kg/day for 28 days, followed by a 28-day recovery period to assess its reversibility, and the study suggested a NOAEL of 500 mg/kg/day for ACC007.

The potential toxicity and toxicokinetics of ACC007 were observed by oral gavage in beagle dogs at doses of 15, 50, and 150 mg/kg/day for 28 days, followed by a 28-day recovery period to assess its reversibility, and the study suggested that the NOAEL of ACC007 was determined to be 150 mg/kg/day.

There was no evidence of genotoxicity of ACC007 in the in vitro mutation test (Salmonella typhimurium revertant mutation test) method according to the guidelines. There was no evidence of genotoxicity of ACC007 in the in vitro

induced chromosome damage test (human peripheral blood lymphocyte chromosome aberration test) performed according to the guidelines. The genotoxicity of ACC007 was assessed by the mouse bone marrow micronucleus test. ACC007 did not cause a significant increase in the incidence of young red blood cell micronuclei in the bone marrow at a single oral dose of up to 2000 mg/kg, suggesting a negative result in the ACC007 mouse bone marrow micronucleus test under the conditions of this study.

1.5 ACC007 Non-clinical Pharmacokinetic Studies

We have mainly conducted studies on the blood concentration-time profile, absorption, distribution, excretion, binding to plasma proteins, biotransformation, drug metabolizing enzymes and drug interactions of ACC007.

Preclinical in vivo data in the species indicate that ACC007 has low plasma clearance, a significantly higher volume of distribution than the extracellular fluid and good oral bioavailability. Extrapolated human PK data suggest that appropriate antiviral concentrations can be achieved with a single daily dose.

After oral administration of [^{14}C]-labeled ACC007 to male mice, most of the elimination of radioactivity occurred within the first 24 hours, mainly through fecal excretion. Within 168 hours of administration, an average of 59.6% of the drug was excreted in the feces and 17.7% in the urine. Radioactivity was widely distributed to mouse tissues throughout the body and showed a time-dependent decrease in all tissues tested. the protein binding of ACC007 was moderate in mouse, canine and human plasma, and the mean percent unbound of ACC007 in humans was 25.2 ± 1.3%.

The metabolic transformation of ACC007 is low in mouse, canine and human liver particles, moderate in monkeys and high in rats, with monohydroxylation being the major in vitro metabolic pathway of ACC007.

In vitro studies of human CYP450 isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4) assays suggest that ACC007 may be slowly metabolically converted via CYP2C19. However, the low metabolic conversion rates of all isoforms suggest that ACC007 is unlikely to cause significant clinical drug interactions based on metabolic inhibition.

ACC007 does not significantly inhibit any of the major human CYP450 isoforms at concentrations up to 25 μM. ACC007 has no induction of CYP1A and a mild induction of CYP3A4. ACC007 is not a substrate for transporter PGP.

1.6 ACC007 Completed Clinical Studies

1.6.1 Tolerability and pharmacokinetics of single dose in healthy Chinese subjects

An open, dose-escalating single-dose administration trial was completed at Beijing Youan Hospital, Capital Medical University, from April 2017 to May 2017, with three dose groups of 75, 150 and 300 mg, 10 cases/group, and no shedding cases among 30 healthy volunteers (20 males and 10 females), all completed the trial to be included in the

safety and pharmacokinetic analysis. The safety, tolerability and pharmacokinetic characteristics of ACC007 were evaluated after a single oral dose on an empty stomach. The study flow is shown in the following figure 1.

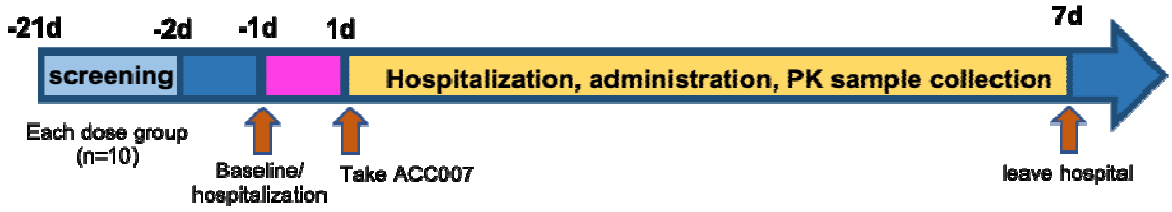

Figure 1 Study Flow of ACC007 Single Dose Tolerability and Pharmacokinetics

Results: The single dose of this product was well tolerated after increasing from 75 mg to 300 mg. Thirty-one adverse events were reported in 17 of 30 subjects (30% in the 75 mg group, 60% in the 150 mg group and 80% in the 300 mg group), of which 26 adverse events were judged as possibly related in 14 of 30 subjects (20% in the 75 mg group, 60% in the 150 mg group and 60% in the 300 mg group). A total of 3 subjects in the 75 mg dose group had 5 adverse events, of which 2 subjects had 4 adverse events judged as adverse reactions, 3 adverse events regressed to disappearance, 1 still existed, and 1 regression was unknown. In the 150 mg dose group, 11 adverse events occurred in 6 subjects, all of which were judged as adverse reactions, 5 adverse events were classified as disappeared and 6 were unknown. In the 300 mg dose group, 15 adverse events occurred in 8 subjects, 11 of which were judged as adverse reactions in 6 subjects, 12 adverse events were classified as disappeared and 3 were still present. Among all the adverse reactions, only one adverse reaction “pre-syncope” in the 150 mg group was judged as grade 2, while the rest were judged as grade 1. Adverse reactions included elevated blood triglycerides, elevated alanine aminotransferase, elevated LDL, elevated aspartate aminotransferase, prolonged activated partial thromboplastin time, positive urine leukocytes, prolonged electrocardiogram QT interval, elevated blood cholesterol, sinus bradycardia, hyperlipidemia, hyperbilirubinemia, and pre-syncope.

Pharmacokinetic analysis showed that ACC007 peaked in humans at T_{max} for about 3h, with slow plasma elimination at $T_{1/2}$ for about 28h, C_{max} and AUC increased with the increase of the dose, but the percentage of increase was lower than the ratio of dose increase. The differences between male and female were not significant. The main pharmacokinetic parameters showed moderate individual variability of this drug.

1.6.2 A trial of the effect of eating on ACC007 in healthy Chinese subjects

An open, randomized, double-crossover design of 150 mg of this product was completed at [redacted] Hospital, [redacted] University, from May 2017 to June 2017. Sixteen subjects (10 males and 6 females) without shedding completed the trial and were included to evaluate and compare the pharmacokinetic parameters and safety of

ACC007 in fasting or fed state. The study flow is shown in the following figure 2.

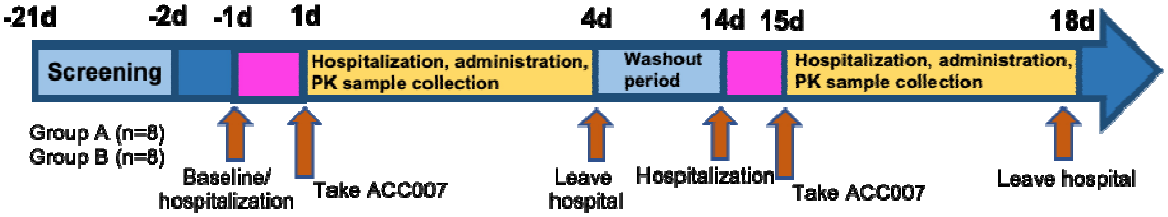

Figure 2 Study Flow for the Effect of Eating on ACC007

Results: A total of 9 adverse events occurred in 7 of 16 (43.8%) subjects during fasting administration period, of which 7 adverse events were judged as adverse reactions in 6 of 16 (37.5%) subjects. Five adverse events turned into disappearance, 1 was relieved and 3 still existed. However, a total of 16 adverse events occurred in 9 of 16 (56.3%) subjects during the postprandial administration period, of which 11 adverse events were judged as adverse reactions in 6 of 16 (37.5%) subjects. Thirteen adverse events turned into disappearance, 1 was relieved and 2 still existed. No serious adverse events or adverse events leading to shedding occurred during the trial. All adverse events were judged as grade 1, and the safety of the subjects was good. The various adverse reactions included elevated alanine aminotransferase, elevated LDL, hematuria, prolonged ECG QT interval, elevated blood cholesterol, elevated blood triglycerides, decreased hemoglobin, sinus bradycardia, sinus arrhythmia, hypertriglyceridemia, dyslipidemia, anemia, and hyperbilirubinemia.

The results of the food effect test showed that diet promoted the absorption of ACC007, increasing C_{max} by >85% and AUC by >20% compared to fasting administration. However, food did not affect the plasma time to peak and plasma elimination half-life of ACC007.

1.6.3 Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple dosing in ART-naïve patients

A multiple dosing safety, tolerability, pharmacokinetic and pharmacodynamic trial was completed at Beijing Youan Hospital, Capital Medical University, from October 2017 to June 2018. The trial was a single-center, continuous dosing, dose-escalation, open trial design with two dose groups of 150 and 300 mg, with 10 subjects in each group. The protocol was later revised to include a 75 mg group of 8 ART-naïve subjects. The study flow is shown in the following figure 3.

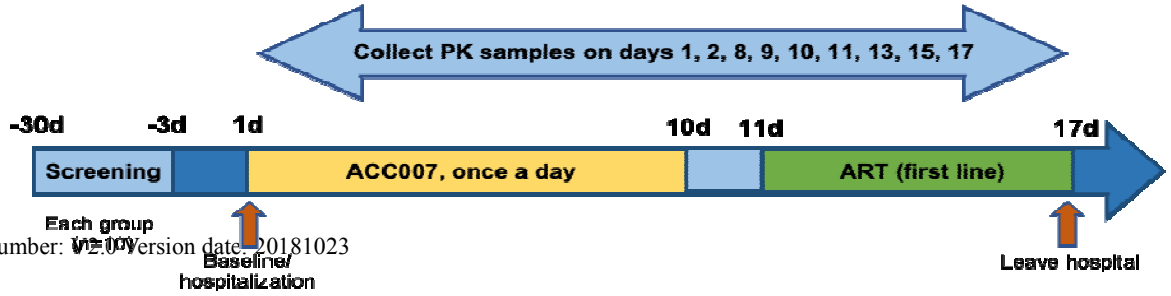

Figure 3 Study Flow of Continuous Dose Escalation Tests of ACC007

Results: During the multiple dosing trial, 17 adverse events occurred in 6 of 8 (75%) subjects in the 75 mg dose group, and 3 adverse events were judged to be adverse reactions in 2 of 8 (25%) subjects, all of which turned into disappearance. In the 150 mg group, 23 adverse events occurred in 8 of 10 (80%) subjects and all were judged as adverse reactions. Thirteen adverse events turned into disappearance, 2 were relieved and 8 still existed. In terms of severity, 5 of the adverse reactions (increased absolute lymphocyte count and increased blood glucose) in 4 subjects were grade 2, and all other adverse reactions were grade 1. In the 300 mg group, 15 adverse events occurred in 7 of 10 (70%) subjects and all were judged as adverse reactions. Four adverse events turned into disappearance, 3 were relieved and 8 still existed. One adverse event (elevated triglycerides) in one subject was judged as grade 3, 2 (elevated blood glucose) were judged as grade 2 in two subjects, and all other adverse events were classified as grade 1. No serious adverse events or adverse events leading to shedding occurred in any of the three groups. The various adverse reactions including: elevated alanine aminotransferase, elevated gamma-glutamyl transferase, decreased white blood cell count, elevated LDL, elevated lymphocyte count, elevated aspartate aminotransferase, decreased blood albumin, elevated blood cholesterol, elevated blood triglycerides, elevated blood uric acid, elevated blood glucose, elevated blood pressure, right bundle branch block, first-degree atrioventricular block, and supraventricular extrasystoles systole.

After 10 days of continuous administration, the dose was increased from 75 mg to 300 mg and the subjects were safe and well tolerated, and the pharmacokinetic parameters increased nonlinearly with the increase of dose. There was no accumulation in the 75 mg, 150 mg and 300 mg groups. The pharmacodynamic results showed a significant decrease in HIV viral load in subjects at 75 mg, 150 mg and 300 mg, with a decrease of 1.73 log10, 1.72 log10 and 1.66 log10, respectively. Both 150 mg and 300 mg dose groups showed good anti-HIV activity.

1.6.4 Clinical study of ACC007 and 3TC+TDF drug interactions

A single-center, sequentially administered, randomized open, parallel, single-order one-way trial was conducted at [redacted] Hospital, [redacted] University, from April 2018 to June 2018. A total of 24 healthy volunteers were included and randomized into two groups (groups A and B) with 12 cases in each group. The study flow of two groups was as follows.

Figure A

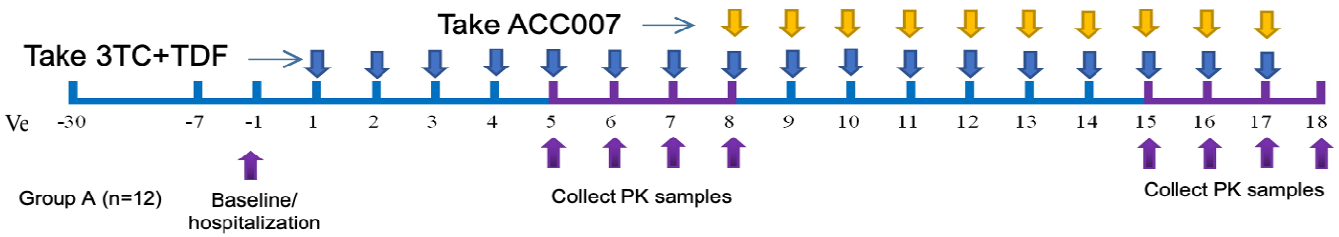

Figure B

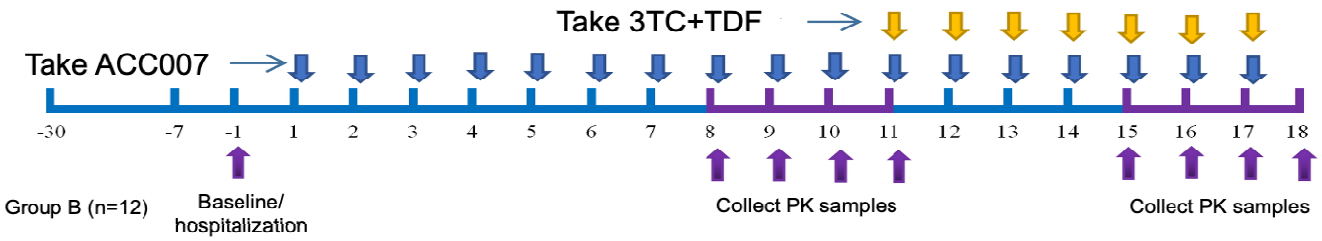

Figure 4 Schematic Diagram of Drug Interaction Research Methods for ACC007 and 3TC + TDF: (A) in Group A; (B) in Group B

Results: During the drug interaction trial, 51 adverse events occurred in 20 of 23 (87%) subjects, 45 of which were adverse reactions to ACC007, including 2 grade 2 adverse events (neutropenia and decreased white blood cell count) and the rest were grade 1. In group A, 24 adverse events occurred in 9 of 12 (75%) subjects, 18 were judged as adverse reactions. Sixteen were turned into disappearance, 4 were relieved, one was aggravated, and one the outcome was unknown. In group B, 27 adverse events occurred in 11of 11 (100%) subjects, which were all judged as adverse reactions. There were 22 adverse events turned into disappearance, 3 were relieved, and 2 the outcomes were unknown. No serious adverse events or adverse events leading to shedding occurred in either group. The various adverse events including: decreased white blood cell count, increased alanine aminotransferase, decreased neutrophil percentage, increased blood creatine phosphokinase MB, decreased neutrophil count, prolonged QT interval on ECG, pharyngitis, upper respiratory tract infection, drowsiness, headache, oropharyngeal pain, rash, fever, febrile sensation, gingival bleeding, nausea, toothache, myalgia, and ventricular extrasystole.

After multiple oral administrations (ACC007 alone/ACC007 combined with 3TC+TDF), the geometric mean ratios of C_{max} and AUC_{ss} for ACC007 were 112.97% and 121.10%, respectively (90 CI%: [redacted] and [redacted], respectively). And (3TC+TDF alone/ACC007 combined with 3TC+TDF), the geometric mean ratios of C_{max} and AUC_{ss} for TDF were 92.47% and 111.24%, respectively (90 CI%: [redacted] and [redacted], respectively). And (3TC+TDF alone/ACC007 combined with 3TC+TDF), the geometric mean ratios of C_{max} and AUC_{ss} were 88.12% and 104.90%, respectively (90 CI%: [redacted] and [redacted], respectively). Taking 80.00%-125.00% as the standard, it shows that ACC007 has weak interaction with 3TC+TDF.

1.7 ACC007, EFV, 3TC and TDF Clinical Studies and Literature Review

1.7.1 Pharmacokinetic Characteristics

1.7.1.1 ACC007

Data from completed clinical studies suggest that, absorption: blood concentrations peak approximately 3 hours after oral administration. Diet promotes absorption of ACC007, with an 86.6% increase in C_{max} and 33.7% increase in AUC_{0-t} compared to fasting administration and no significant differences between the sexes, while the postprandial peak and $T_{1/2}$ remain essentially unchanged. Metabolism: In vitro metabolism studies using human hepatocytes showed that ACC007 is a weak substrate for cytochrome P450 metabolism and that the major isoenzyme involved in metabolism is CYP2C19, which does not induce auto-metabolism. Linearity: The systemic exposure of ACC007 increases with dose-expanding, but disproportionately increased, with a non-linear pharmacokinetic profile. Excretion: The mean renal clearance rate is between 0.11-0.15 L/h, the urinary prototype drug excretion rate is less than 1%, and the plasma clearance half-life is approximately 28 hours.

1.7.1.2 Efavirenz

The results of pharmacokinetic studies of EFV are as follows. Absorption: Plasma concentrations peak after approximately 5 hours of oral administration. Diet promotes the absorption of EFV, and bioavailability increases by 22% and 17% after high-fat or normal meals, respectively, compared to fasting administration. Distribution: EFV is highly bound to human plasma proteins, mainly albumin. Metabolism: Human studies and in vitro studies with human liver microsomes have shown that EFV is metabolized primarily by the cytochrome P450 system to hydroxyl-containing metabolites and their further glucosylated metabolites. These metabolites are essentially inactive against HIV-1. In vitro studies confirmed that CYP3A4 and CYP2B6 are the major isozymes in the metabolism of EFV. In vitro studies also showed that EFV inhibits the P450 isozymes 2C9, 2C19 and 3A4, with weak inhibition at clinically therapeutic doses (Ki values are 8.5-17 μM). And EFV did not inhibit CYP2E1, but only inhibited CYP2D6 and CYP1A2 at doses well above clinical therapeutic doses (Ki values were 82-160 μM). EFV plasma exposure may be increased in patients with the G516T genetic variant of the CYP2B6 isozyme purifier. Moreover, EFV has been shown to induce P450 enzymes, leading to auto-metabolism. Cumulative drug concentrations at doses of 200 to 400 mg daily for 10 days were lower than expected (22 to 42% lower), with an endpoint half-life of 40 to 55 hours, also lower than that of single-dose dosing (52 to 76 hours). Elimination: EFV had a relatively long terminal half-life of 52 to 76 hours for single-dose administration and 40 to 55 hours after multiple doses. Radiolabeled EFV, about 14 to 34% found in urine, and less than 1% of EFV excreted in urine in its original form.

1.7.1.3 Lamivudine

The results of pharmacokinetic studies of 3TC are as follows. Absorption: peak blood concentrations were reached

after approximately 0.9 ± 0.3 hours of oral administration on an empty stomach. Absolute oral bioavailability was 86±16% (mean ± SD) in adult patients. Linear pharmacokinetics in the therapeutic dose range. Concomitant administration with food resulted in a prolongation of T_{max} and a decrease in C_{max} (by 47%). However, absorption was not affected (based on AUC). Distribution: The apparent volume of distribution is approximately 1.3 ± 0.4 L/kg to extravascular tissues. The volume of distribution is independent of dose and body weight. 3TC has a low plasma protein binding rate (less than 36%). In vitro studies have shown that at concentrations of 0.1-100 μg/mL, the binding rate of 3TC to erythrocytes is 53-57%, independent of concentration. Metabolism: Metabolism is a minor route of clearance for 3TC, and the only known metabolite is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of 3TC, 5.2 ± 1.4% of the dose was excreted in the urine as a trans-sulfoxide metabolite, which was not measured in serum. Excretion: The majority of 3TC is excreted from the urine in its original form by active secretion of organic cations. Renal clearance was 199.7 ± 56.9 ml/min (mean ± SD) after a single oral dose of 3TC 300 mg in healthy subjects. In most single-dose studies involving HIV-infected patients, HBV-infected patients or healthy subjects, serum specimens were collected within 24 hours of administration and a mean elimination half-life of 5-7 h was observed, and oral clearance and elimination half-life were independent of dose and body weight at oral doses in the range of 0.25-10 mg/kg.

3TC is cleared primarily as a prototype by renal excretion. Drugs that need to be metabolized in vivo have little potential to interact with 3TC because of its small hepatic metabolism (5-10%) and low binding to plasma proteins.

Studies in patients with renal impairment have shown that the clearance of 3TC is affected by renal insufficiency. Dose adjustment is recommended for patients with creatinine clearance below 20 ml/min. Interaction with meperidine, one of the components of cotrimoxazole, increases 3TC exposure by 40% at therapeutic doses. Dose adjustment is not required unless the patient has renal impairment. Patients with renal impairment require caution with concomitant use of cotrimoxazole and 3TC.

1.7.1.4 Tenofovir Disoproxil Fumarate

The results of the TDF pharmacokinetic studies are as follows. Absorption: TDF is a water-soluble, dual-lipid precursor drug to the active ingredient tenofovir. The oral bioavailability is approximately 25% on an empty stomach. The highest serum concentration (C_{max}) was reached within 1.0±0.4 h after a single oral dose of TDF 300 mg in HIV-1 infected subjects under fasting conditions. C_{max} and AUC_{τ} values were 249 ng/ml and 2541 ng-hr/ml, respectively. After multiple oral administrations of TDF 300 mg on an empty stomach in Chinese healthy subjects, C_{max} and AUC_{τ} values were 328 ng/ml and 2460 ng-hr/ml, respectively. The pharmacokinetics of tenofovir at doses between TDF 75-600 mg

were proportional to the dose and were not affected by repeated dosing. Distribution: In the concentration range of 0.01-25 μg/mL, the in vitro binding of tenofovir to human plasma or serum proteins was less than 0.7% and 7.2%, respectively. The steady-state volume of distribution was 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg after intravenous administration of tenofovir at 1.0 mg/kg and 3.0 mg/kg, respectively. Metabolism and clearance: In vitro studies have shown that neither TDF nor tenofovir is a substrate for CYP enzymes. The terminal half-life of tenofovir after a single oral dose of TDF is approximately 17 h. After multiple oral doses of 300 mg once daily (in the fed state), 32±10% of the administered dose is recovered in the urine within 24 h. Tenofovir is cleared by a combination of glomerular filtration and active renal tubular secretion. Competition for clearance may arise with other drugs that are cleared through the kidney.

1.7.2 Drug Interaction Studies

In vitro and animal results showed that no drug-drug interactions occurred between the three components of this test drug, ACC007, 3TC, and TDF, and no effects on 3TC pharmacokinetic parameters were seen with TDF in healthy volunteers. The results of completed clinical studies of drug interactions with this product indicate a weak interaction between ACC007 and (3TC+TDF).

Because NRTIs are metabolized by different pathways from EFV and are unlikely to compete with EFV for the same metabolic enzymes and elimination pathways, EFV and (3TC+TDF) are not considered to have clinically significant interactions.

1.7.3 Risks of EFV

In clinical controlled studies in combination with PIs and/or NRTIs, the most common adverse events of moderate to severe severity occurring at an incidence greater than 5% and related to treatment were rash (11.6%), dizziness (8.0%), nausea (8.0%), headache (5.7%), and malaise (5.5%). The most notable adverse events associated with EFV were rash, neurologic symptoms, and psychiatric symptoms. Concomitant administration with food increases EFV exposure and can increase the incidence of adverse reactions. Elevations in aspartate aminotransferase, alanine aminotransferase, and glutamyl transpeptidase (GGT) were observed in some laboratory tests performed in clinical studies in some patients receiving EFV. However, the separate GGT elevations in EFV-treated patients respond to enzyme induction rather than hepatotoxicity. Elevated lipids have also been observed in some clinical studies in patients taking EFV. Other treatment-related adverse events that have occurred less frequently in clinical studies include: allergic reactions, coordination abnormalities, ataxia, confusion, coma, dizziness, vomiting, diarrhea, hepatitis, inattention, insomnia, anxiety, heterodreams, sleepiness, depression, abnormal thinking, euphoria, amnesia, confusion,

emotional instability, euphoria, hallucinations, and psychotic symptoms. In addition, some of the adverse events reported in post-marketing surveillance include: neurasthenia, paranoia, cerebellar coordination and balance disorders, convulsions, pruritus, abdominal pain, blurred vision, flushing, gynecomastia, hepatic failure, photosensitivity dermatitis, pancreatitis and redistribution or accumulation of body fat at the back of the neck, breast, abdomen and retroperitoneum, tinnitus and tremors.

1.7.4 Risks of 3TC

The following adverse events have been reported in HIV-1-infected patients treated with 3TC. The adverse events potentially associated with treatment are listed separately according to body system, organ class, and incidence, etc. The conventional expressions for the classification of adverse reactions are: very common (>10%), common (1-10%), rare (0.1-1%), and very rare (<0.01%).

Hematologic and lymphatic system symptoms: neutropenia, anemia (both of which are sometimes severe), thrombocytopenia are rare, and pure red blood cell aplasia is extremely rare; neurologic symptoms include headache, insomnia, and very rarely peripheral neuropathy or sensory abnormalities; respiratory, thoracic, and mediastinal symptoms include cough and nasal symptoms; gastrointestinal symptoms include nausea, vomiting, epigastric pain or abdominal pain, diarrhea, elevated serum amylase, pancreatitis is rare; liver manifestations: rare symptoms are transient elevation of liver enzymes (AST, ALT), and hepatitis is extremely rare; skin and subcutaneous tissue common symptoms are rash, hair loss; musculoskeletal and joint tissue common arthralgia, muscle dysfunction, rhabdomyolysis is rare; other common symptoms are fatigue, discomfort, fever.

Cases of lactic acidosis usually with severe hepatomegaly and fatty liver have been reported in patients on nucleoside analogs, sometimes with life-threatening effects. HIV-1 patients treated with combination antiretroviral drugs can be associated with redistribution of body fat (impaired fat metabolism), including peripheral and facial subcutaneous fat loss, increased abdominal and visceral fat, breast enlargement, and neck and back fat accumulation. Combination antiretroviral therapy may be associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, and hyperlactatemia.

1.7.5 Risks of TDF

In clinical trials with TDF tablets alone or in combination with other antiretroviral drugs in adults with HIV-1 infection, the most common adverse reactions (incidence greater than or equal to 10%, grades 2-4) included rash, diarrhea, headache, pain, depression, malaise, and nausea. In clinical trials of TDF tablets or stavudine in combination with 3TC and EFV in ART-naïve patients, and in clinical trials of TDF + emtricitabine in combination with EFV or

zidovudine/3TC in combination with EFV in ART-naïve subjects as well as ART-experienced subjects, the most common adverse reactions were mild to moderate gastrointestinal events and dizziness. In clinical trials in adult subjects with chronic hepatitis B and compensated liver disease, a higher number of injured subjects experienced nausea, abdominal pain, diarrhea, headache, dizziness, malaise, nasopharyngitis, back pain, and rash. In clinical trials in Chinese adults with chronic hepatitis B, the most frequently reported adverse event was upper respiratory tract infection. In clinical trials in adult subjects with chronic hepatitis B and decompensated liver disease, the most common adverse reactions were abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness and fever. The following adverse reactions were identified during post-approval use of TDF: (1) immune system disorders: allergic reactions, including neuroedema; (2) metabolic and nutritional disorders: hypophosphatemia, hypokalemia, lactic acidosis; (3) respiratory, thoracic and mediastinal disorders: dyspnea; (4) gastrointestinal disorders: abdominal pain, elevated amylase and pancreatitis; (5) hepatobiliary disorders: fatty liver, elevated liver enzymes (most commonly glutamic aminotransferase, ghrelin, gamma-glutamyl transpeptidase), hepatitis; (6) skin and subcutaneous tissue disorders: rash; (7) musculoskeletal and connective tissue disorders: rhabdomyolysis, osteochondrosis (manifested by bone pain, which may cause fractures), myasthenia gravis, myopathy; (8) renal and urinary disorders: renal insufficiency, renal failure, acute renal failure, Fanconi syndrome (renal tubular injury with severe hypophosphatemia), proximal tubular lesions, proteinuria, elevated creatinine, acute tubular necrosis, nephrogenic uremia, polyuria and interstitial nephritis (including acute cases); (9) systemic diseases and medication site conditions: weakness.

2 Objectives of the Study

Primary Objective

- Demonstrate that the proportion of subjects with virologic response (VL < 50 copies/mL) in the ACC007 group is not inferior to the EFV control group at 48 weeks of treatment for HIV/AIDS without ARV, with a non-inferiority threshold of 10%

Secondary Objective

- To evaluate and compare antiviral activity (HIV RNA levels) between the ACC007 and EFV groups at 48 weeks
- To evaluate and compare the safety of the ACC007 and EFV groups at 48 weeks
- To evaluate and compare the changes in immune function (CD4 cell counts) between the ACC007 and EFV groups at 48 weeks
- To evaluate the population pharmacokinetic (popPK) characteristics of ACC007 and PK/PD (PK/HIV

RNA vs. PK/AE) relationship

- To evaluate the safety at 24 weeks of treatment
- To evaluate the proportion of subjects with virological response (VL < 50 copies/mL) at 96 weeks of treatment
- To evaluate antiviral activity (HIV RNA levels) at 96 weeks of treatment
- To evaluate the safety at 96 weeks of treatment
- To evaluate the changes in immune function at 96 weeks of treatment (CD4 cell counts)

3 Study Design and Methodology

3.1 Overall Design

Multicenter, randomized, double-blind, double-simulation, positive parallel-controlled, non-inferiority trial design.

3.2 Sample Size Calculation

According to the literature reports and the current situation of antiviral treatment in China, the average percentage of subjects with HIV RNA levels <50 copies/mL after treatment was expected to be 80% for the experimental group and the control group in this study. The significance level of the test is at a 1-sided, α=0.025, β=0.2, and a non-inferiority threshold is 0.10[3]. Based on the above parameters and a ratio of 1:1 to experimental group and control group, the sample size was calculated to be 252 for each group. After considering the shedding rate of about 20%, the final sample size was calculated to be 630 (315 per group).

3.3 Dose Selection

The results of the completed phase IIa clinical study showed that ACC007 at 75 mg, 150 mg, and 300 mg doses significantly inhibited HIV RNA in infected patients with high or low level of viral loads, with mean viral load decreases of 1.73 log10, 1.72 log10, and 1.66 log10, respectively, and all showed good safety. In view of the results of the ACC007 MAD study showing that its exposure is not linear with the increase in dose, in addition, the 150 mg dose has reached the expected C24 concentration requirements, while the 75 mg dose cannot meet the serum protein-adjusted EC50 (nM) of the K103N/Y181C drug-resistant strain in vitro experiments. Combined with the consideration of the genetic instability of HIV and a combination of drugs with higher exposure concentrations was usually used to prevent the occurrence of drug resistance mutations, the dose of ACC007 administered in this study was therefore determined to be 150 mg per person, once a day.

EFV, 3TC, and TDF have all been on the market for many years and have accumulated a large amount of

evidence-based data on the combination of drugs, and all of them were used in this study at the commonly used clinical doses.

3.4 Study Groups

Table 1 Medication for Study Groups

Group	Experimental drugs	Sample size (Number)	Treatment period (Blind state/week)	Extension period (Open/week)
Test group	Take at night before bedtime: ACC007 150mg + EFV placebo + 3TC 300mg + TDF 300mg	315	48	48
Control group	Take at night before bedtime: EFV 600mg + ACC007 placebo + 3TC 300mg + TDF 300mg	315	48	

Note: At the end of the 48-week study up to week 96, all subjects are no longer taking the placebo and have the option to enter the extension study and continue treatment with ACC007+3TC+ TDF or EFV+3TC+ TDF, or be coordinated for transfer to the National Free Treatment System, depending on the subject's wishes.

4 Subject Selection

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion criteria

(1) 18-65 years old

(2) Diagnosed with HIV-1 infection, HIV RNA ≥ 1000 copies/mL 30 days before enrollment and subject is judged to be suitable for ART regimen by the investigator

(3) Never received ARV treatment or therapeutic HIV-1vaccine and agree not to initiate ART treatment before the baseline visit

(4) Understand and comply with the requirements of the study protocol and voluntarily sign a written informed consent form

4.1.2 Exclusion Criteria

(1) Status of acute HIV-1 infection or currently suffering from AIDS related complex

(2) History of drug abuse, or has a recent history of alcohol/ drug dependence

(3) Any condition considered by the investigator that may compromise the safety of the subject and affect compliance with the study protocol

(4) Participated in a clinical trial with an investigational compound/therapeutic device within 30 days prior to enrollment of this study

(5) Used systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this studyor could not avoid using them during the course of the study

(6) Hepatitis C or hepatitis B with glutathione > 4 times ULN

(7) Creatinine ≥ ULN and a glomerular filtration rate (GFR) ≤ 60 (mL/minute/1.73 m^2) as derived from the $CKD\text{-}EPI_{creatinine}$ formula (GFR = a*(serum creatinine)/b)^c*(0.993)^age. The a values differ according to gender and ethnicity: blacks: females = 166, males = 163; whites and other ethnicities: females = 144, males = 141. The b values differ according to sex: females = 0.7; males = 0.9. The c values differ according to sex and serum creatinine values: females: c = -0.329 for serum creatinine ≤ 0.7 mg/dL, c = -1.209 for serum creatinine > 0.7 mg/dL; males: c = -0.411 for serum creatinine ≤ 0.7 mg/dL, c = -0.411 for serum creatinine > 0.7 mg/dL. (c=-1.209 for serum creatinine > 0.7 mg/dL)

(8) Grade 3 or 4 presentation according to the DAIDS grading scale

(9) Active pulmonary tuberculosis and is on treatment at the time of screening (subjects who develop active pulmonary tuberculosis during the trial will be withdrawn from treatment in order to start anti-tuberculosis therapy)

(10) Received antifungals, corticosteroids, and sulfonamides and antituberculosis drugs within 14 days prior to studyvscreening or taking these drugs.

(11) A history of allergy or hypersensitivity to any component or excipient of the investigational drug

(12) Women who are pregnant or breastfeeding; women of childbearing potential who are not using contraception (e.g., contraceptive diaphragm; condom; IUD, etc.; partner vasectomy) ; female subjects who are unwilling to continue using an investigator-approved form of contraception from screening until 6 months after the last dose of trial drug. Male subjects with active heterosexual sex without vasectomy who are not using birth control methods or who do not wish to continue using contraception during the trial until at least within 30 days after the end of the trial.

4.2 Criteria for Interruption of Treatment

(1) Subjects who are unable to continue observation due to adverse events, or those who are judged by the investigator to need to withdraw from the trial from the perspective of the interests of the subjects, except those who can continue the trial under close observation or corresponding treatment.

(2) Subjects who are found to have failed virological treatment or have serious opportunistic infections during the trial can withdraw from the trial or be transferred to national free ART programme after confirmation by the investigator.

Definition of virological failure: HIV RNA >400 copies/mL after 24 weeks of ART, excluding influencing factors such as poor adherence, drug interactions, and self-malabsorption syndrome. For subjects with virological failure, all plasma samples for viral load and drug resistance testing from baseline to the 24-week visit will be transported to the central laboratory for unified testing. The results of the central laboratory's review and feedback will be used as the criteria for the judgment of virological failure and for further processing.

In the event of virological failure, the principal investigator of each center will decide whether the subject will withdraw from the study and decide the subsequent treatment regimen.

(3) Female subjects were pregnant during the trial.

4.3 Criteria for Withdrawal from the Trial

(1) Subjects who are unable to comply with the trial protocol or the investigator's requirements.

(2) Subjects who are in breach of contract or loss of follow-up

4.4 Criteria for Discontinuing the Trial

Discontinuation of a trial means that the clinical trial has not been completed according to the protocol and all procedures are stopped in the middle. The purpose of trial discontinuation is mainly to protect the rights and interests of subjects, ensure the quality of the trial, and avoid unnecessary economic losses.

Criteria for discontinuing the trial:

(1) In the event of a serious security issue during the trial, the Data and Security Monitoring Board (DSMB) will discuss and decide to discontinue the trial in accordance with the workflow.

(2) Significant errors in the clinical study protocol were found during the trial, making it difficult to evaluate drug effects, or a well-designed protocol had significant deviations in implementation, making it difficult to evaluate drug effects by continuing. Or the quality of the trial does not meet the requirements, and the data recording is inaccurate and incomplete. A resolution to discontinue the trial is made by the DSMB after discussion in accordance with the workflow.

(3) The sponsors requested discontinuation due to funding, unsatisfactory subject recruitment, and administrative reasons.

(4) The State Administration of Market Supervision and Administration requested to suspend the trial.

(5) Discontinuation requested by the ethics committee.

5 Treatment Allocation and Blinding

5.1 Experimental Drugs

ACC007, dosage form: tablet; specification: 75 mg/tablet, 2 tablets each time, once daily; lot number: *******, valid until ******, tested and approved by Jiangsu Aidea Pharmaceutical Co., Ltd.

ACC007 placebo, dosage form: tablet; 2 tablets each time, once daily; lot number: *******, valid until ******, tested and approved by Jiangsu Aidea Pharmaceutical Co., Ltd.

EFV, dosage form: tablet; specification: 600 mg/tablet, 1 tablet/day, lot number: *******, valid until ******, tested and approved, manufactured by Shanghai Disenor Biopharmaceutical Co. and provided free of charge by Jiangsu Aidea Pharmaceutical Co., Ltd.

EFV placebo, dosage form: tablet; 1 tablet each time, once daily; lot number: *******, valid until ******, tested and approved, provided by Jiangsu Aidea Pharmaceutical Co., Ltd.

3TC, dosage form: tablet; specification: 300 mg/tablet, 1 tablet/day; lot number: *******, valid until ******, tested and approved, manufactured by Shanghai Disenor Biopharmaceutical Co.

TDF, dosage form: tablet; specification: 300 mg/tablet, 1 tablet/day, lot number: *******, valid until ******, inspected and qualified, manufactured by Chengdu Bite Pharmaceutical Co., Ltd. and provided by the National Free System.

5.2 Drug Labeling

The following markings will be printed: sponsor name, product name, study number, content, route of administration, storage conditions, lot number and package number, and other regulatory requirements.

For clinical research use only

ACC007 Drugs **for Clinical Trials**

Clinical Study Lot No.: [redacted] Drug Package No.

Product name: ACC007 tablets Verification code.

Specification quantity: 75 mg/tablet, tablet/bottle

Dosage: Take 2 tablets once at night before going to bed

Storage: room temperature, protected from light

Lot number: *******

Effective period: Until ******

Provided by Jiangsu Aidea Pharmaceutical Co., Ltd.

For clinical research use only
Drugs **for EFV clinical trials**
Clinical Study Lot No.: [redacted] Drug Package No.
Product name: Efavirenz tablets Verification code.
Specification quantity: 600 mg/tablet, tablet/bottle
Dosage: Take 1 tablet once at night before going to bed
Storage: room temperature, shade, sealed place
Lot number: *******
Effective period: Until ******
Provided by Jiangsu Aidea Pharmaceutical Co., Ltd.

For clinical research use only
3TC clinical trial drugs
Clinical research lot number: [redacted]
Product name: Lamivudine tablets
Specification quantity: 300 mg/tablet, 30 tablets/bottle
Dosage: Take 1 tablet once at night before going to bed
Storage: room temperature, protected from light
Lot number: *******
Effective period: Until ******
Provided byJiangsu Aidea Pharmaceutical Co., Ltd.

5.3 Drug Storage

ACC007 and its placebo, EFV and its placebo, 3TC, TDF should be stored and transported in a safe place at room temperature and protected from light.

5.4 Drug Allocation and Randomization

The trial was centrally randomized, stratified by center, and random numbers were assigned by DAS for IWRS. Randomization of blinded personnel was performed on a computer using SAS 9.4 statistical software package, and random numbers were generated in a 1:1 ratio between the experimental and control groups using the central zone group randomization method. The randomization numbers were imported into the DAS for IWRS system for requesting randomization numbers and issuing drugs, and each center competed for enrollment. 3TC and TDF were required to keep detailed records of drug allocation and recall. The randomization form (primary blinded base) and secondary blinded base were kept in sealed triplicate and sealed at the sponsor, clinical study agency in charge and DSMB, respectively.

5.5 Subject Code

Each subject was assigned a screening number consisting of a “T” plus 4 digits (e.g., T0001, T0002) according to the signed informed consent form.

5.6 Concomitant Medication

Any other medication taken after administration of the 1st study medication will be considered concomitant medication.

All concomitant medications should be restricted. If concomitant medication is clinically indicated, each drug used must be documented in the CRF. The record information must include: generic name, trade name, route of administration, start date, stop date, dose, and indication. If concomitant drug use occurs, the decision to continue or discontinue participation in the trial will be made by the principal investigator in conjunction with the sponsor.

6 Study Contents and Procedures

6.1 Specific Content for Each Visit Time

6.1.1 Visit 1 (-30d to -1d, screening)

Subjects will be screened 30 days prior to the start of the trial to determine whether meet all inclusion/exclusion criteria. Details are as follows:

(1) Obtain written informed consent.

(2) Collection of subject demographic data and medical history.

(3) Comply with the Health Industry Standard of the People’s Republic of China (WS293-2008) - Diagnostic Criteria for HIV/AIDS.

(4) Record all treatments within the six months prior to enrollment in the study, and if subjects enrolled in the study have used prescription or over-the-counter medications within six months, the investigator should verify their suitability for this study.

(5) HIV confirmation.

(6) Medication adherence education and assessment.

(7) A full physical examination (including height, weight, etc.).

(8) Vital signs: body temperature, respiration, blood pressure and heart rate.

(9) Routine blood test, blood biochemistry, routine urine test.

(10) Hepatitis B screen.

(11) Hepatitis C antibodies.

(12) RPR titers.

(13) Urine drug test screening.

(14) CD4 cell count.

(15) HIV RNA (each center tested its own, as a reference entry criterion).

(16) Ultrasound of the abdomen.

(17) Chest X-rays.

(18) 12-lead electrocardiogram.

(19) Evaluation of inclusion/exclusion criteria.

(20) Combine medication records.

6.1.2 Visit 2 (-7d to 1d, baseline)

(1) Review and record of combined medications.

(2) Medication adherence education and assessment.

(3) Questioning and physical examination.

(4) Vital signs: body temperature, respiration, blood pressure and heart rate.

(5) 12-lead electrocardiogram.

(6) Routine blood test, blood biochemistry, routine urine test.

(7) Urine pregnancy test (women of childbearing age).

(8) CD4 cell count.

(9) HIV RNA (specimens retained for uniform testing in the central laboratory).

(10) Collect plasma for drug resistance test (retain specimens and send them to the central laboratory for uniform testing if necessary).

(11) Evaluation of inclusion/exclusion criteria.

(12) Randomization to the group.

(13) Drug allocation.

6.1.3 Visit 3 (4w±3d)

(1) Review and record of combined medications.

(2) Review and record of adverse events.

(3) Medication adherence education and assessment.

(4) Questioning and physical examination.

(5) Vital signs: body temperature, respiration, blood pressure and heart rate.

(6) 12-lead electrocardiogram.

(7) Routine blood test, blood biochemistry, routine urine test.

(8) CD4 cell count.

(9) HIV RNA (specimens retained for uniform testing in the central laboratory).

(10) Drug recovery and distribution.

6.1.4 Visit 4 (12w±4d)

(1) Review and record of combined medications.

(2) Review and record of adverse events.

(3) Medication adherence education and assessment.

(4) Questioning and physical examination.

(5) Vital signs: body temperature, respiration, blood pressure and heart rate.

(6) 12-lead electrocardiogram.

(7) Routine blood test, blood biochemistry, routine urine test.

(8) Urine pregnancy test (women of childbearing age).

(9) CD4 cell count.

(10) HIV RNA (specimens are kept for uniform testing in the central laboratory; at the same time, each center tested itself once).

(11) PPK specimen collection (record the time of last meal and last medication before this visit and collect fasting blood specimens on the same day and record the collection time, pending unified testing in the central laboratory).

(12) Drug recovery and distribution.

6.1.5 Visit 5 (24w±6d)

(1) Review and record of combined medication use.

(2) Review and record of adverse events.

(3) Medication adherence education and assessment.

(4) Questioning and physical examination.

(5) Vital signs: body temperature, respiration, blood pressure and heart rate.

(6) 12-lead electrocardiogram.

(7) Routine blood test, blood biochemistry, routine urine test.

(8) Urine pregnancy test (women of childbearing age).

(9) CD4 cell count.

(10) HIV RNA (specimens are kept for uniform testing at the central laboratory; at the same time, each center will test once, and if HIV RNA ≥ 50 copies/mL at this visit, all specimens collected to detect viral load and drug-resistant from the baseline to the 24-week visit will be sent to the central laboratory for testing together, and the results of retested HIV RNA will be used as the standard to determine the virological response).

(11) Collect plasma for drug resistance test (retain specimens and send them to the central laboratory for uniform testing if necessary).

(12) PPK specimen collection (record the time of last meal and last medication before this visit and collect fasting blood specimens on the same day and record the collection time, pending unified testing in the central laboratory).

(13) Drug recovery and distribution.

6.1.6 Visit 6 (36w±6d)

(1) Review and record of combined medications.

(2) Review and record of adverse events.

(3) Medication adherence education and assessment.

(4) Questioning and physical examination.

(5) Vital signs: body temperature, respiration, blood pressure and heart rate.

(6) 12-lead electrocardiogram.

(7) Routine blood test, blood biochemistry, routine urine test.

(8) Urine pregnancy test (women of childbearing age).

(9) CD4 cell count.

(10) HIV RNA (specimens retained for uniform testing in the central laboratory).

(11) PPK specimen collection (record the time of last meal and last medication before this visit and collect fasting blood specimens on the same day and record the collection time, pending unified testing in the central laboratory).

(12) Drug recovery and distribution.

6.1.7 Visit 8 (72w±12d)

(1) Review and record of combined medications.

(2) Review and record of adverse events.

(3) Medication adherence education and assessment.

(4) Questioning and physical examination.

(5) Vital signs: body temperature, respiration, blood pressure and heart rate.

(6) 12-lead electrocardiogram.

(7) Routine blood test, blood biochemistry, routine urine test.

(8) Urine pregnancy test (women of childbearing age).

(9) CD4 cell count.

(10) HIV RNA (specimens retained for uniform testing in the central laboratory).

(11) Drug recovery and distribution.

6.1.8 Visit 7 (48w±6d)

(1) Review and record of combined medications.

(2) Review and record of adverse events.

(3) Medication adherence education and assessment.

(4) Questioning and physical examination.

(5) Vital signs: body temperature, respiration, blood pressure and heart rate.

(6) 12-lead electrocardiogram.

(7) Routine blood test, blood biochemistry, routine urine test.

(8) Urine pregnancy test (women of childbearing age).

(9) CD4 cell count.

(10) HIV RNA (specimens retained for uniform testing in the central laboratory).

(11) PPK specimen collection (record the time of last meal and last medication before this visit and collect fasting blood specimen on the same day and record the time of collection, pending unified testing in the central laboratory).

(12) Collect plasma for drug resistance test (retain specimens and send them to the central laboratory for uniform testing if necessary).

(13) Ultrasound of the abdomen.

(14) Chest X-rays.

(15) Drug recovery and distribution.

(16) Fill out the 48-week research summary record form.

At the end of the 48-week study up to week 96, all subjects are no longer taking the placebo agent and may choose to enter the extension study, continue treatment with ACC007 + 3TC + TDF or EFV + 3TC + TDF, or be coordinated for transfer to the national free treatment system, depending on the subject's wishes.

6.1.9 Visit 9 (96w±12d)

(1) Review and record of combined medications.

(2) Review and record of adverse events.

(3) Medication adherence education and assessment.

(4) Interview and physical examination.

(5) Vital signs: body temperature, respiration, blood pressure and heart rate.

(6) 12-lead electrocardiogram.

(7) Routine blood test, blood biochemistry, routine urine test.

(8) Urine pregnancy test (women of childbearing age).

(9) CD4 cell count.

(10) HIV RNA (specimens to be retained for uniform testing in the central laboratory).

(11) Ultrasound of the abdomen.

(12) Chest X-rays.

(13) Collect plasma for drug resistance test (retain specimens and send to the central laboratory for uniform testing if necessary).

(14) Drug recovery.

(15) Fill out the Research Summary Record Form when leave the group.

6.2 Efficacy and Safety Assessment Indicators

6.2.1 General and physical examination

All subjects will be asked about demographic characteristics, medical history, medication compliance, general condition (height, weight), vital signs including blood pressure, heart rate, temperature and respiration, and a complete physical examination before enrollment.

Each visit point after enrollment: In addition to the above examination, we also need to observe the sensory, digestive, cardiovascular, respiratory and neurological changes of the subjects after drug administration, ask about

adverse events and combined medications, and record them in detail.

6.2.2 Laboratory tests.

(1) Routine blood test: red blood cell count (RBC), hemoglobin (HGB), red blood cell ratio (HCT), mean red blood cell ratio (MCV), mean red blood cell hemoglobin content (MCH), mean red blood cell hemoglobin concentration (MCHC), platelet count (PLT), total white blood cell count, and sorted count (WBC, LYMPH, MONO, NEUT, EOS, BASO),etc.

(2) Routine urine test: pH, specific gravity (SG), urine glucose (U-GLU), urine protein (PRO), urine bilirubin (UBG), bilirubin (BIL), urine white blood cell count (LEU), urine ketone bodies (KET), urine red blood cells (RBC),etc.

(3) Urine pregnancy test (only women of childbearing age tested),etc.

(4) Blood biochemical tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl aminotransferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), serum amylase (AMY), total bilirubin (TBIL), direct bilirubin (DBIL), blood glucose (Glu), blood uric acid (UA), urea nitrogen (BUN), blood creatinine (CREA), cholesterol (CHOL), triglyceride (TG), total protein (TP), albumin (ALB),etc.

(5) CD4 cell count.

(6) HIV-1 viral load measurement.

(7) Hepatitis B markers (HBV-M, including HBsAg, HBsAb, HBeAg, HBeAb, HBcAb).

(8) Hepatitis C virus antibody (anti-HCV).

(9) Syphilis titer (RPR titer).

(10) Urine test to confirm drug abuse (including morphine, methamphetamine, ketamine, dimethylenedioxymethamphetamine, tetrahydrocannabinfenic acid, etc.).

(11) 12-lead electrocardiogram.

(12) Ultrasound of the abdomen.

(13) Chest X-ray examination.

6.2.3 Pharmacogenetic specimen collection

Pharmacogenic specimens from all subjects will be retained by sparse sampling method, and the population pharmacokinetic characteristics and PK-PD and PK-AE correlations of ACC007 will be assessed after uniform testing.

Table 2 Pharmacogenetic Specimen Collection Schedule

Visiting Viewpoints	Study days/week	Collection time

4	12W	Fasting
5	24W	Fasting
6	36W	Fasting
7	48W	Fasting

Note: PK specimens will be collected at 12, 24, 36, and 48 week visits on an empty stomach and the time of PK collection will be recorded, along with the time of last meal and last dose of medication.

6.3 Efficacy Indicators and Quality Control of Central Laboratory Tests

6.3.1 Detection of HIV viral load

Whole blood collected in accordance with the "SOP for Specimen Collection, Preparation, and Cryopreservation" during the screening period and at 12 and 24 weeks of the study will be separated and prepared for plasma, and will be tested by each research center. The test results at the screening period will be used as the inclusion criteria for subjects, and the test results at 24 weeks will be used as the reference standard for assessing virological failure.

From the beginning of the baseline to the end of the study, each blood collection time should collect 10 mL of whole blood from the subjects according to the SOP of Specimen Collection, Preparation, Freezing and Transfer, and the plasma after separation and preparation should be divided into lyophilization boxes and stored in the refrigerator at -80°C. The lyophilization boxes should be marked with the project name, lyophilization box number, and the range of the sample corresponding to the random number. The top view of the specimen in the lyophilization box should be filled in to find the specimen, and the collected specimens should be transferred to the central laboratory. The transfer and testing of viral load specimens (HIV RNA Abbott) in the central laboratory should be performed in full compliance with the SOP for transfer and testing of specimens to strictly control possible bias in this major efficacy index.

6.3.2 Detection of CD4

In -30d~-1d, -7d~1d, the CD4 cell count should be checked once each, and a total of two tests will be performed, and the last test result will be used as the baseline value of CD4. Testing is required at each study center at each visit time from 4 weeks to the end of the study.

6.3.3 Detection of PPK

At 12, 24, 36 and 48 weeks of the study, each blood collection time should collect 4.5 mL of whole blood according to the SOP for PPK specimen collection, preparation, freezing and transfer, and the plasma after separation and preparation should be stored in 3 portions in lyophilization boxes at -80°C in the refrigerator until the analysis test, and avoid repeated freezing and thawing. The specimens collected should be transferred to the pharmacogenetic

specimen testing agency. The transfer and testing of PPK specimens by the pharmacogenetic specimen testing agency should be carried out in full compliance with the SOP for the transfer and testing of specimens in the central laboratory in order to strictly control the possible bias of this major efficacy index.

6.3.4 Genotypic drug resistance testing

At baseline and at 24 weeks, 48 weeks and 96 weeks of treatment, each blood collection time should collect 10 mL of whole blood according to the SOP for collection, preparation, preservation and transfer of genotypic drug resistance test specimens. After separation and preparation, the plasma should be stored in 3 portions in a lyophilization box at -80°C until analysis and testing when necessary. The top view of the specimen in the lyophilization cassette can be used to locate the specimen.

6.4 Efficacy Assessment

6.4.1 Primary endpoint indicators

- Percentage of subjects with HIV RNA levels <50 copies/mL at 48 weeks of treatment (RT-PCR method), evaluated by Snapshot Approach[4].

6.4.2 Secondary endpoint indicators

- Changes in HIV RNA log values at 48 and 96 weeks of treatment
- Percentage of HIV RNA levels ≤400 copies/mL at 48 and 96 weeks of treatment
- Percentage of subjects with HIV RNA levels <50 copies/mL at 96 weeks of treatment
- Changes in CD4 cell counts at 48 and 96 weeks of treatment

6.5 Safety Assessment

6.5.1 Clinical Safety Assessment

Subjects' spontaneous reports or direct physician observation or non-induced questioning of subjects about adverse events will be collected during the clinical trial and evaluated at 24, 48 and 96 weeks of treatment.

6.5.2 Laboratory Safety Assessment

The changes of routine blood test, routine urine test, blood biochemistry and electrocardiogram at 24, 48 and 96 weeks will be compared, and urine pregnancy test (only for women of childbearing age), abdominal ultrasound and chest X-ray will be performed during the clinical trial to evaluate their safety.

6.6 PK/PD (PK/HIV RNA, PK/AE) Assessment

According to the population pharmacokinetic method, the analysis of drug PK/PD and PK/AE relationships will be

performed by sparse sampling to obtain blood concentrations with the main efficacy and safety indicators.

6.7 Medication Adherence Assessment

Adherence assessment (%) = actual number of medications/theoretical number of medications × 100%.

Medication adherence assessment: ACC007 or EFV and (3TC + TDF) will be calculated separately for compliance.

This study required medication adherence of ≥90% and ≤110%.

7 Drug Safety Management

7.1 Develop a Drug Safety Management Plan

The drug safety vigilance department of the sponsor or its delegated institution will develop a drug safety management plan based on GCP-related principles and clinical trial-related content (e.g., protocols, investigator manuals, literature, etc.) that will document, describe, and define the various tasks of drug safety management as a guide to the entire drug safety management process. The drug safety management plan should include: communication plan, drug safety management time plan, drug safety management process, report review, and document maintenance.

7.2 Adverse Events

7.2.1 Definition of adverse event

An adverse medical event that occurs after a subject receives a drug, but is not necessarily causally related to treatment. Adverse events include, but are not limited to:

- Abnormal laboratory test results.
- Clinically significant signs and symptoms.
- Changes in physical examination results.
- Allergies.
- Progression/exacerbation of pre-existing disease.

In addition, adverse events include signs or symptoms resulting from:

- Drug overdose.
- Discontinuation of medication.
- Drug abuse.
- Drug misuse.
- Drug-drug interactions.

- Drug dependence.

7.2.2 Abnormal laboratory test results

The criteria for determining whether an abnormal objective finding should be reported as an adverse event are as follows:

- The test result correlates with concomitant symptoms, and/or
- The test result requires additional diagnostic testing or therapeutic measures/surgical intervention, and/or
- The test results lead to a change in the subject's drug dose or discontinuation of the trial, the need for additional concomitant medication, or other treatment, and/or
- The investigator or sponsor judged that the test result should be reported as an adverse event.

If it is only to repeat the examination of an abnormality, but does not meet any of the above conditions, it will not be judged as an adverse event. Any abnormal test result that is judged to be an error is not required to be reported as an adverse event.

7.2.3 Observation of adverse event

All observed or spontaneously reported adverse events must be tracked by investigators with sufficient information to determine the consequences of the adverse events and assess whether they meet the criteria for serious adverse events and require immediate reporting to appropriate personnel and departments.

For all adverse events, the investigator should also obtain sufficient information to clarify the cause of the adverse event and to make an assessment of the cause of the adverse events. If the investigator believes that there is a causal relationship between the trial drug and the adverse event, the adverse event must be followed until the adverse event or its sequelae have resolved or stabilized at a level that the investigator considers acceptable.

7.2.4 Reporting period

From the time after the subject's first dose of the trial drug until the last follow-up visit, the investigator shall report all directly observed adverse events as well as subject voluntarily reported adverse events. In addition, each subject will be asked questions about the adverse event.

All adverse events should be recorded on the adverse event page of the case report form, with adverse event terminology and accurate medical terminology, and coded according to the MedDRA Code system.

7.2.5 Adverse event severity assessment

The investigators graded the adverse events according to the DAIDS AE grading scale (if an adverse event

occurred that is not covered by the DAIDS AE grading scale, please refer to CTCAE v5.0) into grades 1 to 5, where grade 1 corresponds to mild, grade 2 corresponds to moderate, grade 3 corresponds to severe, grade 4 corresponds to potentially life-threatening, and grade 5 corresponds to death.

A distinction should be made between the severity and seriousness of the adverse event, and a severe adverse event may not be a serious adverse event.

7.2.6 Evaluation of the relationship between adverse events and trial drugs

The investigator must make an assessment of the cause of all adverse events (serious and non-serious). This assessment is the investigator's judgment of the likelihood that the test drug caused or was involved in causing the adverse event. If the investigator is uncertain about the cause of the adverse event and does not know whether it was caused by the trial drug, the event should be classified as "related to the trial drug". If the investigator's assessment is "unknown cause but not related to the trial drug", the event should be clearly documented in the trial record.

The relationship between clinical reactions and laboratory abnormalities and test drugs will be evaluated according to the following five levels, the first three were counted as adverse reactions, and the incidence of adverse reactions should be counted.

Definitely related

The reaction occurs in a reasonable chronological order of administration, is consistent with the type of reaction known for the suspected drug, disappears after discontinuation of the suspected drug, and the subject's clinical status or other reasons are unlikely to produce the reaction.

Likely related

The reaction occurs in a reasonable chronological order of administration, is consistent with the type of reaction known for the suspected drug, is significantly reduced after discontinuation of the suspected drug, and the subject's clinical status or other reasons are unlikely to produce the reaction.

Possibly related

The reaction occurs in a reasonable chronological order of administration, is consistent with the type of reaction known for the suspected drug, and can be alleviated after stopping the suspected drug, but the subject's clinical status or other reasons may also produce the reaction.

Possibly unrelated

The reaction does not appear in a reasonable chronological order after administration, does not correspond well to the type of reaction known for the suspected drug, does not alleviate after discontinuation of the suspected drug, the

subject's clinical state or other causes may have produced the reaction, and the reaction is alleviated after improvement of the disease state or elimination of other causes.

Definitely not related

The reaction does not occur in a reasonable time sequence after administration, does not correspond to the type of reaction known for the suspected drug, the subject's clinical state or other causes can produce the reaction, and the reaction is reduced after the disease state improves or other causes are eliminated.

7.3 Serious Adverse Events

7.3.1 Definition of serious adverse event (SAE)

A serious adverse event is any undesired medical event that occurs at any dose, including:

- Results in death.
- Is life-threatening (The subject was at risk of death at the time of the event).
- Requires inpatient hospitalization (other than hospitalization due to social factors) or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Other important medical events: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Medical and scientific judgment should be exercised in determining whether an event is a medically significant event. An important medical event, although not necessarily immediately life-threatening and/or resulting in death or hospitalization, should be reported as a serious adverse event if it is determined to be potentially harmful to the subject and requires medical intervention to prevent the occurrence of any of the consequences in the definition of serious adverse event above.

7.3.2 Serious adverse event reporting

If a serious adverse event occurs during the trial, regardless of whether it is related to the trial treatment, appropriate treatment measures must be taken immediately, along with reporting by telephone, faxing the serious adverse event report form to the principal investigator within 24 hours of being informed.

If a serious adverse event occurs, the investigator should report the event to the sponsor, the drug clinical trial institution and ethics committee of the study center, the State Administration of Market Administration (formerly CFDA), the provincial Food and Drug Administration, the National Health and Family Planning Commission, the DSMB, and the pharmacovigilance department of the sponsor or its delegated institution within 24 hours of becoming aware of the event, and the investigator must sign and date the report.

If a serious adverse event occurs that is fatal or life-threatening, the appropriate personnel and departments should be notified immediately, regardless of how much information on this adverse event has been obtained. This time limit also applies to additional information about a previously reported serious adverse event. If the investigator is unable to learn of the serious adverse event in a timely manner (e.g., if the patient is seen in an outside hospital), but should report and document when he/she first learned of the adverse event within 24 hours of becoming aware of it.

For all serious adverse events, it is the responsibility of the investigator to track and provide information to the appropriate personnel and departments in accordance with the reporting timelines specified above. This information should be more detailed than the information recorded on the adverse event report form. Typically, a detailed description of the adverse event should be included so that a complete medical assessment of the event can be made and an independent determination of the probable cause can be made. In addition, information on other possible causes, such as concomitant medications and concomitant diseases, must also be provided. In the case of death of a subject, the autopsy report, if available, must be forwarded to the appropriate personnel and authorities as soon as possible.

The drug safety alert department of the sponsor or its delegated agency shall report the serious adverse event report to the State Administration of Market Supervision (formerly CFDA), the National Health and Family Planning Commission, the Provincial Food and Drug Administration, and the Provincial Health and Family Planning Commission within the 7-day (death or life-threatening SAE)/15-day (other SAE) period after receipt of the serious adverse event report form.

Each serious adverse event reported by the investigator during the clinical trial is to be reviewed by the sponsor's pharmacovigilance staff in a timely manner to determine if it is a suspected and unexpected serious adverse reaction (SUSAR). If a SUSAR is judged to be a fatal/life-threatening event, it will be sent to the pharmacovigilance department of the sponsor 2 business days prior to the reporting deadline (7 calendar days), and the remaining SUSARs will be sent to the pharmacovigilance department of the sponsor 2 business days prior to the reporting deadline (15 calendar days), in accordance with ICH "E2B(R3): Management of Clinical Safety Data: Transmission of Individual Safety Reports", and the relevant terms should be coded using the ICH "M1: Medical Dictionary for Regulatory Activities (MedDRA)".

SUSAR does not include:

（1）Non-serious adverse events.

（2）Serious adverse event determination may or may not be related to the trial drug ACC007.

（3）Serious but expected adverse reactions.

（4）Should remain blind as much as possible, but in the broken blind state, can be judged as definitely related, likely related or possibly related to EFV, 3TC, TDF, and meet the expected adverse reactions of EFV, 3TC and TDF.

（5）AIDS and AIDS-related complications.

The CRA is responsible for properly recording and maintaining all SAEs, regularly verifying and updating them, and communicating with the investigators to urge them to follow up the SAEs on time. The CRC enters the SAEs and report tracking data into the EDC system in a timely manner, and the data management agency regularly summarizes and reports them to the sponsor, who sends them to the CRA for uniform reporting to the investigators, drug clinical trial institutions and ethics committees of each participating center.

7.4 SAE Reports Contact Information

Table 3 SAE Reporting Contact Information Form

Participant	Unit Name		Contact person	Contact number	Reporting method/email/address
Drug regulatory authorities[1]	State Administration of Market Supervision and Administration (former CFDA)		NA	010-68313344	Fax: 010-88363228 / Address: Building 2, No. 26 Xuanwumen West Street, Xicheng District, Beijing, 100053
	National Health and Family Planning Commission		NA	010-68792776	Fax: 010-68792734 / Address: No.1 Xizhimenwai South Road, Xicheng District, Beijing, 100044, P.R. China
Research Center[1]	Beijing Youan Hospital, Capital Medical University	Principal Investigator	Wu Hao	[redacted]	E-mail.whdoc@sina.com Address: No.8 Xitoujiao, Youanmenwai, Fengtai District, Beijing

		Drug clinical trial institutions	Wang Meixia	010-83997181	wangmeixiad@163.com
		Ethics Committee	Sheng Aijuan	010-83997028	youanlunli@126.com
DSMB	Tangdu Hospital of Xi'an Fourth Military Medical University	President	Sun Yongtao	029-84777910	yongtaos@hotmail.com
Applicant	Jiangsu Aidea Pharmaceutical Co., Ltd.		Shen Xiaoning	18705185597	chris.sheng@wmtc.com.cn
Pharmacovigilance department	Beijing Zhiji Pharmaceutical Information Consulting Co., Ltd.		Ou Yi	13717870071	ouyi2013@163.com

Note: 1: Provincial drug supervision and management departments and health planning committees, other research centers to report contact information for details see drug safety management plan.

7.5 Consistency Verification of Serious Adverse Events

From the enrollment of the first subject, the consistency of SAE reporting records with the safety data recorded in the clinical trial data of EDC is verified according to the drug safety management plan data management plan, and further investigation and follow-up reports are required to ensure that no SAE is missed or misreported.

7.6 Pregnancy Incident Reporting

In the event of pregnancy in the subject or the subject's sexual partner, the investigator must report the pregnancy to the sponsor or its delegated safety manager within 24 hours of being informed and deal with it accordingly according to the drug safety management plan established for this project.

8 Quality Control

8.1 Monitoring, Audit and Inspection

- Monitoring: The monitor will visit the study center regularly to monitor the trial, including checking case report forms, verifying original records, and conducting and recording drug counts. The monitor will also observe the progress of the trial and discuss any problems with the investigator in order to resolve

them in a timely manner.

- Audit: The sponsor will designate a person to conduct an audit at each research center.
- Inspection: The State Administration of Market Supervision and Administration may conduct inspection of this test.

8.2 Identification of Subjects

All screened subjects will be registered by number.

8.3 Retention of Original Records

According to GCP requirements, the study centers should retain all subject information for a period of 5 years after the trial is fully completed. If the trial drug is approved for marketing, the retention period is 5 years after the trial drug is approved for marketing.

8.4 Internal Quality Control and Quality Assurance

To ensure compliance with the requirements of this trial protocol and the GCP, the sponsor will commission the CRO monitor to conduct screening, enrollment sites, and periodic monitoring visits during the course of the trial. The investigators and research institutions should allow direct access to the original documents by the monitors and inspectors to complete the verification.

The IEC and/or the sponsor's quality assurance auditors may verify the raw data.

The investigator and relevant personnel should be involved throughout the monitoring visits, possible audits and inspections.

In addition, the internal quality control officer of the research agency will conduct occasional random checks on the whole process and data information of this test to ensure that this trial is conducted in strict accordance with the trial protocol.

9 Data Management

9.1 Develop a Data Management Plan

The data manager develops a data management plan based on GCP-related principles and clinical trial-related elements (e.g., plan, CRF draft, actual situation of the project, etc.). The data management plan will document, describe and define the data management tasks to guide the entire data management process. The data management plan should include: data management process, eCRF design, data entry and challenge management, external data management,

database locking, document retention, etc.

9.2 eCRF Design

The eCRF design will be carried out according to the research proposal. After the eCRF design is completed, a system test is required. The eCRF after the test is completed and approved by the sponsor will be put into operation.

9.3 Data Entry

The eCRF data are obtained from the original records and are entered into the EDC by the investigator or authorized personnel in a timely manner according to the instructions for completing the eCRF to ensure that the data are true, accurate, complete, and timely, and that they are consistent with the data in the subject's original medical record. The investigator's EDC user name and password are for the exclusive use of the investigator and should not be disclosed, and should not be used by others to enter data on behalf of the investigator.

9.4 User Management

All users accessing the EDC are required to fill out a user account application form, and after the PM confirms approval, the project administrator user application form creates the roles of investigator, research assistant (CRC), etc. and grants different permissions to access the EDC. e.g., investigators in each center can only see the content of their own center and have the right to revise data, and sponsors are limited to browsing the EDC; monitors can read the EDC data in each center and have no data revision The supervisor can read the EDC data of each center without data revision rights, but can issue questions.

All users who access EDC need to fill in the account application form. After confirmation and approval by PM, the project administrator will create roles such as researcher and research assistant (CRC) and grant different permissions to access EDC. Among them, the researchers of each center can only see the content of their own center and have the right to revise the data. The sponsor is limited to browsing the EDC. The monitor can read the EDC data of each center and ask questions, but has no data revision authority.

9.5 Data Verification

On-site verification of source data: The supervisor performs consistency checks between eCRF data and source data, and can send questions if there are problems.

Data verification plan: The data manager develops the verification plan based on the program and eCRF. Online verification program is configured according to the data verification plan, and data queries are automatically generated by the system, while queries can also be sent manually during manual data checking.

Data questions and answers: Questions come from system questions of EDC logic verification, and manual questions such as auditors and data administrators, which need to be answered by researchers in a timely manner. Data administrators and monitors close the queries and can reissue them if necessary until the data is “clean”.

9.6 Electronic Signature

After data entry is completed and no data doubts after on-site verification of source data, the investigator conducts electronic signature review and confirmation. If there are data revisions after the signature, a new signature is required.

9.7 Database Locking

After the database lock record is signed by the principal investigator, sponsor, statistical analyst and data manager, the data manager performs the database locking.

9.8 Data Management File Retention and Data Transfer

The project data manager shall maintain data management related documents as required and transfer the locked database to the statistical analyst for statistical analysis.

10 Statistical Analysis

10.1 Hypothesis Testing

H0 (null hypothesis): $P1-P2 \leq -0.1$, H1 (alternative hypothesis): $P1-P2 > -0.1$

P1 is the viral load suppression rate in the experimental group, and P2 is the viral load suppression rate in the control group. Viral load suppression rate is that the proportion of subjects achieving HIV RNA < 50 copies/mL.

10.2 Analysis Sets

Full analysis set (FAS): a collection of all subjects who are randomized into the study and have received at least one dose of study drug. When the primary efficacy indicators are missing, the previous result will be carried forward according to the intentional analysis. Secondary efficacy indicators were will be according to the actual data in the FAS.

Per-protocol analysis set (PPS): a data set generated from subjects who are fully compliant with the trial protocol. Adherence includes treatment received, availability of index measurements for the primary endpoint, and no major violations of the trial protocol. The PPS will be used for the primary efficacy analyses.

Safety data set (SS): received at least one treatment and have the actual data recorded by the safety index after treatment. The incidence of adverse reactions will be used as the denominator for the number of SS cases.

10.3 Statistical Analysis Methods

10.3.1 48 weeks after treatment

The new drug application shall be based on the 48-week clinical study data summary report of the confirmatory trial.

10.3.1.1 Case enrollment analysis

List the number of cases screened, enrolled, and completed overall and at each center, and determine four data sets for analysis (FAS, PPS, SS).

List the number of cases screened overall and by center, the number of cases that failed screening, and their causes and rates.

List the number of cases that were not included in the analysis set and their reasons.

Calculate the number of cases enrolled, completed the trial, and terminated the trial early, as well as their reasons and rates.

Draw the flow chart of subject distribution.

List the number and percentage of subjects with mild and severe breaches/deviations from the protocol.

10.3.1.2 Demographic information and baseline analysis

Statistical description of demographic data and other baseline characteristics.

- Continuous variables will calculate means, standard deviations, quartiles, minimum and maximum values.
- Enumeration data and ranked data will calculate frequency and composition ratio.
- All data will be analyzed using actual data in FAS, and baseline data of efficacy indicators will be added the PPS analysis.

10.3.1.3 Analysis of medication adherence and coadministration

The actual data in FAS and PPS will be used for the analysis.

Medication adherence:

- Calculate the percentage of subjects with medication adherence in the range of 90-110%.
- Drug exposure dose.
- Duration of drug exposure.

Combination of medications:

- Calculate the percentage of subjects with combined medications.
- Combined medication ATC classification analysis.

- Combinations are divided into pre-treatment combinations and post-treatment combinations, coded according to WHO Drug.

10.3.1.4 Efficacy analysis

Analysis of the primary efficacy indicators:

- The percentage of subjects with viral load less than 50 copies/mL after 48 weeks of treatment will be analyzed by PPS and FAS at the same time. With baseline HIV RNA <100000 copies/mL and ≥100000 copies/mL as independent variables, and viral load suppression rate as response variable, logistic regression analysis will be performed to compare the differences between groups as well as calculate its two-sided 95% confidence interval. Then, whether the experimental group is non-inferior to the control group will be judged according to a pre-set non-inferiority criterion of 10%. According to the Snapshot Approach recommended by FDA, HIV RNA missing data during the window period will be treated as no virological response and considered as HIV RNA ≥ 50 copies/mL.

Analysis of secondary efficacy indicators:

- The difference between the log value of HIV RNA after 48 weeks of treatment and the baseline value will be analyzed by covariance analysis (ANCOVA) with the group as a fixed effect and the baseline value as a covariate. PPS and FAS analyses will be performed at the same time.
- The percentage of subjects with HIV RNA ≤ 400 copies/mL after 48 weeks of treatment will be also analyzed by PPS and FAS. With baseline HIV RNA <100000 copies/mL and ≥100000 copies/mL as independent variables, and viral load suppression rate as response variable, logistic regression analysis will be performed to compare the differences between groups. According to the Snapshot Approach recommended by FDA, HIV RNA missing data during the window period will be treated as no virological response and considered as HIV RNA ≥ 50 copies/mL.
- The difference between the CD4 cell count after 48 weeks of treatment and the baseline value will be analyzed by covariance analysis (ANCOVA) with group as a fixed effect and baseline value as a covariate. CD4 cell counts will be carried forward with the previous results when they were missing at the window period, 24 weeks and 48 weeks as recommended by the FDA. PPS and FAS analyses will be performed at the same time.

10.3.1.5 Safety Analysis

- SS will be used for safety analysis.
- Adverse events will be coded according to the ICH International Dictionary of Medical Terms (MedDRA 21.0, Medical Dictionary for Regulatory Activities).
- Calculate the incidence of Treatment Emergent Adverse Event (TEAE)/reactions, serious adverse events/reactions, and adverse events/reactions leading to shedding during treatment.
- List the number and frequency of adverse events/reactions, significant adverse events/reactions, serious adverse events/reactions, adverse events/reactions leading to shedding by SOC and PT during treatment, and calculate the incidence.
- List the number and frequency of adverse events/reactions, significant adverse events/reactions, serious adverse events/reactions, adverse events/reactions leading to shedding by SOC and PT during treatment according to different severity, and calculate the incidence.
- List a detailed list of various adverse events/reactions, significant adverse events/reactions, serious adverse events/reactions, and adverse events/reactions leading to shedding.
- List the cross-tabulation of laboratory and ECG indices for clinical significance determination before and after medication administration.
- List cases of abnormal laboratory, electrocardiogram, and physical examination indicators and clinical explanations after drug administration.
- Vital signs actual measurements change over time.

10.3.2 96 weeks after treatment

For subjects entering the extension study, the efficacy analysis will be performed using FAS and the safety analysis will be performed using SS. The analysis includes efficacy, safety, and adherence to drug administration. Methods same as 48 weeks.

10.3.3 PK/PD (PK/HIV RNA, PK/AE) analysis

See the PK/PD analysis plan for details.

10.4 Statistical Software and General Requirements

SAS 9.4 software will be used for analysis.

All statistical tests will be performed using a two-sided test, and P values less than or equal to 0.05 would be considered statistically significant.

Unless otherwise specified, the decimal places of the minimum and maximum values are consistent with the

original data recorded in the database, the decimal places of the mean and quartiles are retained one decimal place more than the original data, and the standard deviation is retained two decimal places more than the original data. The maximum number of decimal places for all statistical data is not more than four.

Percentage (%): 1 decimal place is retained and the second place is rounded off, e.g. 52.34% is recorded as 52.3%.

11 Data Retention

11.1 Electronic Data Recording

In accordance with the EDC system, eCRF will be used as the data collection method for this study.

It is the responsibility of the investigator to ensure timely completion, verification and approval of the eCRF. eCRFs must have the electronic signatures (i.e., account passwords) of authorized investigators. These electronic signatures are to certify that the information recorded in the eCRF is authentic. It is the ultimate responsibility of the investigator to ensure the accuracy and authenticity of all clinical and laboratory data recorded in the eCRF at all times.

11.2 File Preservation

The subject's original file, the subject's file recorded by the investigators, will be kept at the study center.

To ensure evaluation and/or audit by pharmacovigilance authorities or sponsors, investigators maintain files that include the identity of all subjects enrolled in the trial (with adequate information linked to the file, e.g., study medical and/or hospitalization records), all original informed consents, original documentation, and detailed records of treatment. The investigator should maintain the file for the longest period of time required therein, as agreed in the regulations or clinical trial protocol.

12 Trial Summary

The clinical trial data of each center will be summarized and uniformly analyzed by the statistical agency to form a statistical report.

The summary form will be completed by the Phase III clinical trial sub-center.

The principal investigator of the group leader agency will complete the clinical trial summary report in accordance with the statistical report and be audited by the National Center for Clinical Trial Evaluation of Pharmaceuticals, which will be stamped with the official seal and be handed over to the sponsor after approval.

13 DSMB Responsibilities and Program Modifications

13.1 DSMB Responsibilities

To maximize the protection of subjects' interests and ensure the validity and integrity of the data, the sponsor established the Data and Safety Monitoring Boards (DSMB) for clinical trials and formulated the DSMB Charter for this trial in accordance with WHO guidelines. The DSMB Charter ensures that the DSMB can provide an independent, valid, and timely review of data and make decisions without bias during the study. DSMB responsibilities are as follows:

(1) Monitoring study execution

- Overall and center-by-center enrollment rates, noncompliance, poor-adherence, program violations, and disengagement.
- Data integrity and timeliness.
- The degree of agreement between the study center's assessment of the event and the centralized assessment.
- Enrollment in important subgroups: HIV RNA <100000 copies/mL and ≥100000 copies/mL.

(2) Review of clinical safety data

- All Grade 3 or higher adverse events (as determined by the NIH DAIDS AE grading scale)
- SAE.
- All adverse events with an incidence >2%.

(3) Review of clinical efficacy data

(4) Recommendations to sponsors and principal investigators

- Notification of adverse events and serious adverse events.
- Suggested changes that should be made to the study protocol.
- Recommendations to suspend or terminate a study.

13.2 Program Modification

After this protocol has been approved by the Ethics Committee, the DSMB has the right to propose changes to the study protocol to the sponsor and the principal investigator, after which the sponsor and the principal investigator of the responsible agency will write the revised protocol and submit it to the Ethics Committee for approval before it can be implemented.

14 Contact Address and Phone Number of the Sponsor and Each Study Center

1) Sponsor

Jiangsu Aidea Pharmaceutical Co., Ltd..

Address: No.2, Liuzhuang Road, Ganjiang District, Yangzhou City, China. Postcode: 25008

Tel: 0514-87530666 Fax: 0514-87752666

2) Group Leader Agency

01 Beijing Youan Hospital, Capital Medical University

Address: No.8 Xitoujiao, Youanmenwai, Fengtai District, Beijing, China. Postcode: 100069

Tel: 010-83997961 Fax: 010-63057511

3) Participating Agencies

02 Beijing Ditan Hospital, Capital Medical University

Address: No. 8, Jingshun East Street, Chaoyang District, Beijing, China. Postcode: 100015

Tel: 010-84322581 Fax: 010-84322581

03 Guangzhou Eighth People's Hospital

Address: No. 627 Dongfeng East Road, Guangzhou, China. Postcode: 510060

Tel: 020-83822580 Fax: 020-83828329

04 Infectious Disease Hospital of Henan Province

Address: No.29 Jingguang South Road, Jinshui District, Zhengzhou City, Henan Province, China. Postcode: 450061

Tel: 0371-60331665 Fax: 0371-60331665

05 The First Hospital of Changsha

Address: No.311 Yingpan Road, Kaifu District, Changsha, Hunan Province, China. Postcode: 450061

Tel: 0731-82223156 Fax: 0731-82223156

06 Chongqing Public Health Medical Center

Address: No.109, Glorious Hill Conservation Road, Shapingba District, Chongqing, P.R. China. Postcode: 400036

Tel: 023-65503066 Fax: 023-65503066

07 The Second Hospital of Nanjing

Address: No.1 Rehabilitation Road, Tangshan Street, Jiangning District, Nanjing, China. Postcode: 211113

Tel: 025-85091722 Fax: 025-85091722

4) Pharmacogenetic Analysis and Testing Agency

Chinese Academy of Sciences Shanghai Institute of Materia Medica

Address: 501 Haike Road, Shanghai, China. Postcode: 201210

Tel: 021-50800738 Fax: 021-50800738

5) Data Management Agency

Beijing Zhiji Pharmaceutical Information Consulting Co., Ltd.

Address: 01-312, 8F, No.18 Zhongguancun Street, Haidian District, Beijing, China. Postcode: 100190

Tel: 010-58648971 Fax: 010-58648971

6) Statistical Analysis Agency

Beijing Bozhiyin Technology Co., Ltd.

Address: Room 2-2209, Timesail Building, No.15 West Majiapu Road, Beijing, China. Postcode: 100068

Tel: 010-67587407 Fax: 010-68451871

7) Clinical Trial Monitoring Agency

Beijing Co-CRO Medical Development Co., Ltd.Address: Room 1288, Red Building, No.46 Dongsi West Street, Beijing, China. Postcode: 100711

Tel: 010-85116590 Fax: 010-85116590

15 References

[1] Li H, Zhang FJ, Lu HZ, et al. Expert consensus on the management of patients with HIV infection co-infected with chronic kidney disease[J]. China AIDS STD, 2017(6):578-580.

[2] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017].

[3] Martins M, Cahn P E, Lopardo G D, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48- week results of a randomised, double-blind, phase 3, non-inferiority trial[J]. Lancet Hiv, 2018.

[4] FDA, Guidance for Industry Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment, 2013.