CLINICAL STUDY PROTOCOL

Virologic Outcomes of Lamivudine/Dolutegravir in Virologically suppressed subjects with Expected or confirmed Resistance to Lamivudine (VOLVER Study)

Sponsor: Fundación SEIMC-GESIDA

Protocol code: GESIDA 11820

Nº EduraCT: 2021-000290-84

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Version of Protocol: 4.0

Date of Protocol: 31. May. 2021

Confidential information

PROTOCOL SIGNATURE PAGE

Study Title: Virologic Outcomes of Lamivudine/Dolutegravir in Virologically suppressed subjects with Expected or confirmed Resistance to Lamivudine (VOLVER study).

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Signature of the Coordinating Investigators:

Dr José Ramón Arribas - La Paz University Hospital

Name	Signature	Date

Dr Federico Pulido - 12 de Octubre Hospital

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Signature of the sponsor:

Dr Juan Julián Gonzalez García - Chairperson of the Board of Directors

Name	Signature	Date

Signature of the Principal Investigator:

Name: **Site:**

Name	Signature	Date

1. SUMMARY

I. Sponsor: Fundación SEIMC-GESIDA

II. Clinical study title: Virologic Outcomes of Lamivudine/Dolutegravir in Virologically suppressed subjects with Expected or confirmed Resistance to Lamivudine (VOLVER study).

III. Principal Investigators:

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IV. Clinical study phase: IIa.

V. Team participants:

Multicentre study, to be conducted at 17 healthcare centres in Spain. The listing of all investigators and sites will be attached in a separate document**.**

VI. Background:

Dolutegravir (DTG) plus lamivudine (3TC) is a dual regimen combination recommended for both naïve and suppressed persons with HIV-1 infection[1]. However, data regarding the efficacy of this regimen in suppressed persons with history of past resistance or virologic failures is currently insufficient. In particular, it is important to determine if this combination is safe to use in persons with past resistance to 3TC. Limited data from retrospective cohorts, and a small number of participants from the DOLULAM and TANGO studies seem to point that DTG/3TC may be used without exposing individuals

to a significant risk of virologic failure, despite historical 3TC resistance or archived minority 3TC resistance-associated mutations [2–5]. In our prospective pilot study ART-PRO[6] 18/21 persons with past M184V/I mutations, not detected at baseline through proviral DNA Sanger sequencing, were switched to DTG/3TC and maintained virologic control for 96 weeks without any case of virologic failure[7]. In our study, archived 3TC-resistance associated mutations were detected at baseline through next-generation sequencing (NGS) over the 5% threshold in more than half of participants with past 3TC resistance, without any detrimental effect on viral control. Although showing promising results, ART PRO study's generalizability is limited due to the small size and the exclusion of participants exposed to integrase inhibitors, which call for a larger study. VOLVER study aims to enrol persons with confirmed or suspected history of 3TC resistance and demonstrate that, when proviral DNA population sequencing no longer detects 3TC resistance-associated mutations, DTG/3TC is sufficient to maintain virologic suppression. Based in our prior findings, we also want to confirm that the virological impact of 3TC-resistant archived minority variants prior to switching to DTG/3TC is negligible in this context.

VII. Study design:

Phase IIa, open-label, single arm, multicentric study. Follow up: 96 weeks.

VIII. Study treatment:

Dovato® (Dolutegravir 50 mg/Lamivudine 300 mg film-coated tablet):

Route of administration: oral.

Dose: Dolutegravir 50 mg/Lamivudine 300 mg/day.

Posology: one 50 mg/300 mg film coated-tablet once daily.

Intervention: change of current antiretroviral treatment to DTG 50 mg/3TC 300 mg QD.

IX. Study Locations:

This is a multicentre study, and it will be conducted at different healthcare centres in Spain. The listing of all investigators and sites where the clinical trial is going to be conducted is attached in a separate document

X. Estimated sample size:

120 participants. A minimum of 30%-50% of the study population would be required to have historical RNA population genotype with confirmed M184V/I mutation.

XI. Ethics Committee:

The study will be evaluated by the Ethics Committee (Comité de Ética de la Investigación con medicamentos) of University Hospital La Paz which is authorized by the Ministry of Health and Consumer Affairs (https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/listado -comites-investigacion-clinica.pdf) and by the health authorities of the Autonomous Community of Madrid (Spain).

XII. Hypothesis:

Our hypothesis is that therapy with DTG/3TC would be able to maintain viral control in HIV infected participants with prior history of 3TC resistance but without evidence of M184V/I resistance mutation in proviral DNA population sequencing at baseline. We also hypothesize that archived minority 3TC resistance associated mutations detected by next-generation (NGS) sequencing prior to the switch would not have a significant impact on the efficacy of DTG/3TC.

XIII. Study Objectives and Endpoints:

Primary objective	**Primary endpoint**
To assess the efficacy of a switch to DTG/3TC for maintenance of virologic suppression at 48 weeks in persons with past confirmed or suspected 3TC resistance, when proviral DNA population sequencing does not detect 3TC resistance-associated mutations at baseline.	Proportion of virologic failure (VF) defined as HIV-1 RNA viral load (VL) ≥ 50 copies per mL at 48 weeks (in the intention-to-treat-exposed population (ITT-e) using the US Food and Drug Administration (FDA) snapshot algorithm).
Secondary objectives	**Secondary endpoints**
To evaluate other estimations of virological control at weeks 48 and 96.	- Proportion of VF (≥50 copies/mL) at week 96, ITT-e, FDA snapshot. - Proportion of VF (≥50 copies/mL) at week 48 and 96, per protocol population (PP), FDA snapshot. - Proportion of VF (≥200 copies/mL) at week 48 and 96, ITT-e and PP population,

	FDA snapshot. - Proportion of Confirmed Virologic Withdrawal ([CVW]: A VL≥ 50 copies/mL followed by a VL≥ 200 copies/mL in re-test) at weeks 48 and 96, ITT-e and PP population, FDA snapshot. - Proportion of Precautionary Virologic Withdrawal ([PVW]: three consecutive VL between 50- 200 copies/mL) at weeks 48 and 96, ITT-e and PP population, FDA snapshot. - Proportion of participants with VL<50 copies/mL week 48 and 96, ITT-e and per protocol population, FDA snapshot.
To assess viral resistance in persons experiencing VF.	- Incidence of VF with drug resistance associated mutations. - Describe number and type of resistance-associated mutations in VF

To evaluate factors associated with VF.	- Analysis of factors associated to VF (i.e time to VF).
	- Proportion of VF in pre-specified subgroups:
	  - Confirmed historical M184V/I vs No resistance mutations
	  - INSTI exposure vs No prior INSTI exposure
	  - Time virologically suppressed
	  - Time on 3TC/FTC

To assess the impact of baseline archived minority 3TC resistance-associated mutations in viral control (in cases of VF and transient viral rebounds [VL≥50copies/mL preceded and followed by VL<50 copies/mL]).	- Proportion of participants with VF with baseline 3TC or INSTI resistance-associated mutations detected at baseline by NGS with 1, 5, and 20% threshold. - Proportion of participants with transient viral rebounds with baseline 3TC or INSTI

	resistance- associated mutations detected at baseline by NGS with 1, 5, and 20% threshold.
To evaluate the dynamics of archived minority 3TC resistance-associated mutations after switching to DTG/3TC at 96 weeks.	Type and frequency of resistance mutations (RT and integrase) in proviral DNA measured by NGS at baseline and week 96.
To evaluate the immune effects of switch to DTG/3TC	Change from Baseline in $CD4^+$ cell count and in $CD4^+/CD8^+$ cell counts ratio at weeks 48 and 96
To evaluate the safety and tolerability of DTG/3TC in this study	- Incidence and severity of AEs and laboratory abnormalities through week 48 and 96. - Proportion of subjects who discontinue treatment due to AEs through weeks 48 and 96.

XIV. Disease under study: HIV-1 infection.

XV. Study population:

Persons receiving antiretroviral treatment, followed at study participating centres.

Inclusion Criteria:

a. Adults (≥ 18 years old) with HIV-1 infection able to understand and give informed written consent.
b. Stable ART in the 12 weeks prior to screening visit.
    - Only switch for tolerability/convenience/access reasons to generic drugs or switch from ritonavir to cobicistat or TDF to TAF would be allowed in the 12-week window and as long as the components of the regimen are unchanged.
c. Viral load <50 copies/mL at screening and in the year prior to study entry.
    - A blip (50-500 copies/mL) would be allowed within 48 weeks prior to inclusion in the study, if preceded and followed by an undetectable VL determination.
d. $CD4^+$ count > 200 cells/µL at screening.

e. History of 3TC resistance: either *confirmed historical 3TC resistance* (historical RNA Sanger or RNA NGS>20% threshold genotype with M184V/I mutation) OR *suspected historical 3TC resistance.*
   - Suspicion of past 3TC resistance is defined as <u>any</u> of the following:
     i. Previous treatment with only 2 NRTIs (1 of them being emtricitabine or 3TC [XTC]).
     ii. Two consecutive VL > 200 copies/mL while on treatment including XTC.
     iii. One VL > 200 copies/mL while on treatment including XTC <u>PLUS</u> change of ART as consequence of that elevated VL.

<u>Exclusion Criteria:</u>

a. Participants with M184V/I or K65R in screening visit proviral DNA Sanger genotype.
b. Prior virologic failure (VF) under integrase inhibitor (INSTI)- based regimen. defined as two consecutive VL > 200 copies/mL while receiving INSTI regardless of genotypic test results
c. INSTI resistance mutations in historical RNA genotype.
d. Documented resistance to DRV defined as the presence of a combination of mutations scored with at least 15 points in the Stanford University HIV Drug Resistance Database.
e. Positive Surface Hepatitis B Ag (HBAgS) OR negative HBAgS and negative hepatitis B surface antibody (anti-HBs) with positive anti-core antibody (anti-HBc) and positive HBV DNA.
f. Pregnant, breastfeeding women, women with a positive pregnancy test at the time of screening, sexually active fertile women wishing to conceive or unwilling to commit to contraceptive methods (see Appendix 1 for the accepted list of the highly effective methods for avoiding pregnancy), for the duration of the study and until 4 weeks after the last dose of study medication. All women are considered fertile unless they have undergone a sterilizing surgery or are over the age of 50 with spontaneous amenorrhea for over 12 months prior to study entry.

g. Patients with active opportunistic infections or cancer requiring intravenous treatment and/or chemotherapy at screening.
h. Any comorbidities or treatment with experimental drugs that according to the investigator could bias study results or entail additional risks for the participant.
i. Participants receiving other medications that according to study drug label are contraindicated.
j. Severe hepatic impairment (Class C) as determined by Child-Pugh classification.
k. Alanine aminotransferase (ALT) over 5 times the upper limit of normal (ULN) or ALT over 3xULN and bilirubin over 1.5xULN.
l. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (apart from hyperbilirubinemia or jaundice due to Gilbert's syndrome or asymptomatic gallstones);
m. Creatinine clearance of <30 mL/min/1.73m^2 via CKD-EPI method.
n. Any verified Grade 4 laboratory abnormality that to the investigators criteria would affect the safety of the participant if included in the study.
o. History or presence of allergy to dolutegravir or lamivudine.

XVI. Duration of the study:

i. Duration of the participant selection period: 9 months.
ii. Duration of the follow-up period: 96 weeks.
iii. Data analysis and preparation of the final report: 6 months.

2. INDEX

3. GENERAL INFORMATION

3.1 Study identification

Clinical study title: Virologic Outcomes of Lamivudine/Dolutegravir in Virologically suppressed subjects with Expected or confirmed Resistance to Lamivudine (VOLVER study).

3.2 Type of clinical study

Phase IIa, open-label, single arm, multicentric study. Follow up: 96 weeks.

3.2 Study drug description

Dovato® (Dolutegravir 50 mg/Lamivudine 300 mg film-coated tablet):

Route of administration: oral.

Dose: Dolutegravir 50 mg/Lamivudine 300 mg/day.

Dosage: one 50 mg/300 mg film-coated tablet once daily.

Intervention: change of current antiretroviral treatment to DTG 50 mg/3TC 300 mg QD.

3.3 Principal investigators

Dr. José Ramón Arribas López
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12 de Octubre University Hospital.
Av. Cordoba s/n. 28041-Madrid
e-mail: federico.pulido@salud.madrid.org

3.4 Collaborating centres

Multicentre study, to be conducted at 17 healthcare centres in Spain. The listing of all investigators and sites will be attached in a separate document.

3.5 Monitor identification

Fundación SEIMC-GESIDA.

C/ Agustín de Betancourt, 13-Entreplanta.

Tel: +34 91 556 80 25

Fax: +34 91 554 22 83

email: secretaria@f-sg.org

3.6 Ethics committee of reference identification

Hospital La Paz Research Ethics Committee (Comité Ético de Investigación Clínica, CEIC).

Paseo de la Castellana, 261, 28046 Madrid.

e-mail: ceic.hulp.@salud.madrid.org

3.7 Expected duration

After obtaining the approval of the study by La Paz Research Ethics Committee (Comité Ético de Investigación Clínica) and by the Spanish Agency for Medicines and Health Products (Agencia Española del Medicamento, AEMPS), it is intended to carry out the study according to the following work plan:

i. Duration of the participant selection period: 9 months.
ii. Duration of the follow-up period: 96 weeks.
iii. Data analysis and preparation of the final report: 6 months.

4. BACKGROUND AND JUSTIFICATION

DTG/3TC is a dual regimen combination recommended for both naïve and suppressed persons with HIV-1 infection[8]. With the advent of DTG/3TC single tablet, a massive roll out of this antiretroviral therapy combination could be expected. Yet, data in treatment-experienced persons with past VF or resistances is currently insufficient to guarantee the robust benefits that DTG/3TC has already proved in large multicentric studies including naïve and suppressed persons without past resistances[2,9].

3TC resistance-associated mutations are frequent in persons with past VF, with prevalence ranging from 34 to 96% depending on the setting, and the 2019 WHO HIV drug resistance report listing the M184V mutation as the most frequent mutation

associated with acquired NRTI drug resistance [10–12]. A retrospective study analysing 32,440 retrotranscriptase (RT) sequences of treatment-experienced persons found that about one third had codon 184 substitutions[13]. However, our group has demonstrated that 3TC resistance-associated mutations may not be detectable overtime as proviral DNA in suppressed persons detected only 26.9% of past M184V/I mutations[14]. At present, it is still unknown if proviral DNA genotyping in virologically suppressed patients can predict the efficacy of a given treatment, as this assay may not detect all previously existing drug-resistance mutations[15–17]. The importance of detecting minority resistant populations in proviral DNA is even more questionable since a high proportion of archived HIV is non replicating[18,19]. In addition, there is currently very little information on the relevance of those minority resistant populations detected by NGS, but not through proviral DNA population sequencing. To our knowledge, no study has prospectively investigated the dynamics of archived minority resistant variants in the presence of the drug to which they are theoretically resistant.

Studies in virologically failing patients have shown that 3TC retains antiviral efficacy despite evidence of 3TC resistance-associated mutations[20–22]. The MOBIDIP study was the first trial evaluating a dual regimen including 3TC for maintenance of HIV suppression in persons with history of 3TC resistance-associated mutations. In said study, 265 virologically suppressed participants- 96% of whom had a historical genotype detecting the M184V mutation- were randomized to either boosted protease inhibitor monotherapy or to 3TC plus boosted protease inhibitor. The study was prematurely discontinued after 48 weeks because the proportion of VF with boosted protease inhibitor monotherapy was significantly higher compared to 3TC plus boosted protease inhibitor (difference between groups 21.8%)[11]. Considering these results and in the context of past 3TC resistance, it is reasonable to contemplate that combining 3TC to another drug with a high genetic barrier such as DTG would also succeed in maintaining virologic suppression.

Reintroducing 3TC paired with DTG has shown promising results as maintenance therapy in persons with past 3TC resistance. The current scarce evidence for this strategy comes mostly from retrospective cohort analysis, a small number of participants from the DOLULAM study and four participants from the TANGO study who were found

to have the M184V mutation in proviral DNA at baseline and remained with virologic suppression through 48 weeks[3–5,23].

The only study prospectively evaluating the efficacy of DTG/3TC in suppressed persons with past 3TC resistance is our pilot study ART-PRO[6], where we hypothesized that this combination would be effective in maintaining virologic control in integrase naïve persons if 3TC resistance-associated mutations were not detected on baseline proviral DNA Sanger sequencing. In our study, 18/21 persons with past M184V/I mutations, not detected at baseline through proviral DNA Sanger sequencing, were switched to DTG/3TC and have maintained virologic control for 96 weeks without any case of VF[7]. The three participants that did not reach week 96 were discontinued due to a DTG-related insomnia and two protocol violations, where two participants included in the study had baseline M184V mutation and thus were prematurely removed from the study at week 12, despite sustaining undetectable VL (<50 copies/mL). Interestingly, archived 3TC-resistance associated mutations were detected at baseline through NGS over the 5% threshold in more than half of participants with past 3TC resistance, without any detrimental effect on viral control. Although showing promising results, ART-PRO study's generalizability is limited due to the small size and the exclusion of participants exposed to integrase inhibitors.

Reusing 3TC in persons with past resistance combined with DTG would not only open the possibility to recycle 3TC but would also allow access to a simplified regimen endorsed by guidelines in participants who, owing to previous VF, are frequently excluded from clinical studies and treated with complex antiretroviral combinations that may include high pill burden or risk of toxicity. Therefore, we believe it is reasonable to perform a fully powered study designed to confirm the initial favourable results of our pilot study ART-PRO.

5. HYPOTHESIS AND OBJECTIVES

5.1 Hypothesis

Our hypothesis is that therapy with DTG/3TC would be able to maintain viral control in HIV infected participants with prior history of 3TC resistance but without evidence of M184V/I resistance mutation in proviral DNA population sequencing at baseline. We

also hypothesize that archived minority 3TC resistance associated mutations detected by next-generation (NGS) sequencing prior to the switch would not have a significant impact on the efficacy of DTG/3TC.

5.2 Objectives

Primary objective	Primary endpoint
To assess the efficacy of a switch to DTG/3TC for maintenance of virologic suppression at 48 weeks in persons with past confirmed or suspected 3TC resistance, when proviral DNA population sequencing does not detect 3TC resistance-associated mutations at baseline.	Proportion of virologic failure (VF) defined as HIV-1 RNA viral load (VL) ≥50 copies per mL at 48 weeks (in the intention-to-treat-exposed population (ITT-e) using the US Food and Drug Administration (FDA) snapshot algorithm).
Secondary objectives	**Secondary endpoints**
To evaluate other estimations of virological control at weeks 48 and 96.	- Proportion of VF (≥50 copies/mL) at week 96, ITT-e, FDA snapshot. - Proportion of VF (≥50 copies/mL) at week 48 and 96, per protocol population (PP), FDA snapshot. - Proportion of VF (≥200 copies/mL) at week 48 and 96, ITT-e and PP population, FDA snapshot. - Proportion of Confirmed Virologic Withdrawal ([CVW]: A VL≥ 50 copies/mL followed by a VL≥ 200 copies/mL in re-test) at weeks 48 and 96, ITT-e and PP population, FDA snapshot. - Proportion of Precautionary Virologic Withdrawal ([PVW]: three consecutive VL between 50- 200 copies/mL) at weeks 48 and 96, ITT-e and PP population, FDA snapshot. - Proportion of participants with VL<50 copies/mL week 48 and 96, ITT-e and per

	protocol population, FDA snapshot.
To assess viral resistance in persons experiencing VF.	- Incidence of VF with drug resistance associated mutations. - Describe number and type of resistance-associated mutations in VF

To evaluate factors associated with VF.	- Analysis of factors associated to VF (i.e time to VF).
	- Proportion of VF in pre-specified subgroups:
	  - Confirmed historical M184V/I vs No resistance mutations
	  - INSTI exposure vs No prior INSTI exposure
	  - Time virologically suppressed
	  - Time on 3TC/FTC

To assess the impact of baseline archived minority 3TC resistance-associated mutations in viral control (in cases of VF and transient viral rebounds [VL≥50copies/mL preceded and followed by VL<50 copies/mL]).	- Proportion of participants with VF with baseline 3TC or INSTI resistance-associated mutations detected at baseline by NGS with 1, 5, and 20% threshold. - Proportion of participants with transient viral rebounds with baseline 3TC or INSTI resistance- associated mutations detected at baseline by NGS with 1, 5, and 20% threshold.
To evaluate the dynamics of archived minority 3TC resistance-associated mutations after switching to DTG/3TC at 96 weeks.	Type and frequency of resistance mutations (RT and integrase) in proviral DNA measured by NGS at baseline and week 96.
To evaluate the immune effects of switch to DTG/3TC	Change from Baseline in $CD4^+$ cell count and in $CD4^+/CD8^+$ cell counts ratio at weeks 48 and 96
To evaluate the safety and tolerability of DTG/3TC in this study	- Incidence and severity of AEs and laboratory abnormalities through week 48 and 96.

	- Proportion of subjects who discontinue treatment due to AEs through weeks 48 and 96.

*Intention- to -treat-exposed (ITT-e) includes all participants receiving at least one dose of DTG/3TC.

**Per protocol (PP) analysis excludes participants with protocol violations, lost to follow-up and those with low adherence (adherence at or below the 2.5th percentile of those in the study).

6. TYPE OF CLINICAL STUDY AND DESIGN

6.1 Clinical study phase

Phase IIa study.

6.2 Study design

Open, single-arm, multicentric study evaluating the efficacy and safety of DTG/3TC as maintenance therapy for HIV-1 virologic suppression in persons with historical 3TC resistance.

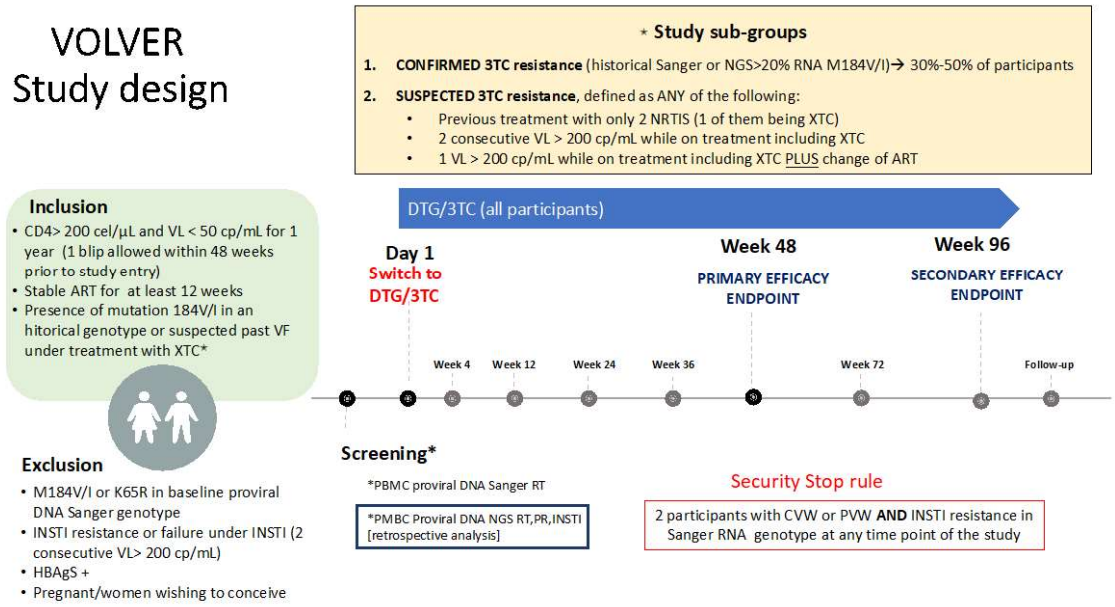
The study consists of a Screening phase (maximum 60 days prior to day 1), and a Switch phase (day 1).

The study will screen for adult participants with HIV infection with history of confirmed or suspected resistance to 3TC receiving stable ART for at least 12 weeks and virologically supressed for at least one year prior to the study entry. Participants who provide informed consent and meet inclusion criteria will be screened in order to enrol 120 subjects.

On day 1 all participants who meet study entry criteria will be switched to DTG/3TC. There will be two groups: one group with confirmed historical 3TC resistance mutation, that is, with the M184V/I in an historical RNA Sanger genotype (minimum 30%-50% of the study population), and another group with suspicion of 3TC resistance based on clinical and virological history. No participant with M184V/I or K65R detected in screening proviral DNA population sequencing will be allowed to enter the study. Participants will attend study centres at screening, baseline, weeks 4, 12, 24, 36, 48 (primary efficacy endpoint), 72 and 96 (secondary efficacy endpoint, end-of-study visit). Primary endpoint is proportion of virologic failure at 48 weeks, following the FDA snapshot algorithm, ITT-

e analysis. There will be a safety analysis at week 24 and also a “stopping rule” throughout the study, whereby if two cases of confirmed (CVW) or precautionary virologic withdrawal (PVW) occur *with INSTI resistance at any timepoint*, the study will be terminated (see section 7.4 for definitions for CVW and PVW). Procedures described in this protocol will be performed at each visit, including blood sampling for hemogram, biochemistry, HIV viral load and CD4 count. At screening and week 96, proviral DNA NGS will be performed. RNA sanger genotype and proviral DNA NGS will be performed in all cases of CVW and PVW.

Overall study design:



This study will be conducted in compliance with the protocol, Good Clinical Practice, and all applicable regulatory requirements.

7. PARTICIPANT SELECTION

Subjects will be offered to participate in the study on the basis of the following eligibility criteria.

7.1 Inclusion criteria

a. Adults (≥ 18 years old) with HIV-1 infection able to understand and give informed written consent.
b. Stable ART in the 12 weeks prior to study entry.
    - Only switch for tolerability/convenience/access reasons to generic drugs or switch from ritonavir to cobicistat or TDF to TAF would be allowed in the 12-week window and as long as the components of the regimen are unchanged.
c. Viral load <50 copies/mL at screening and in the year prior to study entry.
    - A blip (50-500 copies/mL) would be allowed within 48 weeks prior to inclusion in the study, if preceded and followed by an undetectable VL determination (HIV-RNA <50 copies/mL).
d. $CD4^+$ count > 200 cells/µL at screening.
e. History of 3TC resistance: either *confirmed historical 3TC resistance* (historical RNA Sanger or RNA NGS>20% threshold genotype with M184V/I mutation) OR *suspected historical 3TC resistance.*
    - Suspicion of past 3TC resistance is defined as <u>any</u> of the following:
        i. Previous treatment with only 2 NRTIs (1 of them being emtricitabine or 3TC [XTC]).
        ii. Two consecutive VL > 200 copies/mL while on treatment including XTC.
        iii. One VL > 200 copies/mL while on treatment including XTC <u>PLUS</u> change of ART as consequence of that elevated VL.

7.2 Exclusion criteria

a. Participants with M184V/I or K65R in screening visit proviral DNA Sanger genotype.
b. Prior virologic failure (VF) under integrase inhibitor (INSTI)- based regimen. defined as two consecutive VL > 200 copies/mL while receiving INSTI regardless of genotypic test results
c. INSTI resistance mutations in historical RNA genotype

d. Documented resistance to DRV defined as the presence of a combination of mutations scored with at least 15 points in the Stanford University HIV Drug Resistance Database.
e. Positive Surface Hepatitis B Ag (HBAgS) OR negative HBAgS and negative hepatitis B surface antibody (anti-HBs) with positive anti-core antibody (anti-HBc) and positive HBV DNA.
f. Pregnant, breastfeeding women, women with a positive pregnancy test at the time of screening, sexually active fertile women wishing to conceive or unwilling to commit to contraceptive methods (see Appendix 1 for the accepted list of the highly effective methods for avoiding pregnancy), for the duration of the study and until 4 weeks after the last dose of study medication. All women are considered fertile unless they have undergone a sterilizing surgery or are over the age of 50 with spontaneous amenorrhea for over 12 months prior to study entry.
g. Patients with active opportunistic infections or cancer requiring intravenous treatment and/or chemotherapy at screening.
h. Any comorbidities or treatment with experimental drugs that according to the investigator could bias study results or entail additional risks for the participant.
i. Participants receiving other medications that according to study drug label are contraindicated.
j. Severe hepatic impairment (Class C) as determined by Child-Pugh classification.
k. Alanine aminotransferase (ALT) over 5 times the upper limit of normal (ULN) or ALT over 3xULN and bilirubin over 1.5xULN.
l. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (apart from hyperbilirubinemia or jaundice due to Gilbert's syndrome or asymptomatic gallstones);
m. Creatinine clearance of <30 mL/min/1.73m^2 via CKD-EPI method.
n. Any verified Grade 4 laboratory abnormality that to the investigators criteria would affect the safety of the participant if included in the study.
o. History or presence of allergy to dolutegravir or lamivudine.

7.3 Estimated sample size

In previous studies of switch to DTG/3TC the rate of VF at week 48 has been 0.7%[24]. With 120 participants recruited, and considering the same proportion of VF, we could rule out differences in the proportion of VF > 4% with a binomial estimation of the 95% confidence interval (power 80%, alpha 5% bilateral).

There will be two groups of participants: one with *confirmed* history of 3TC resistance based on historical RNA genotype and another one with *suspected* 3TC resistance based on clinical and virologic history. The group with confirmed 3TC resistance will comprise at least between 30-50% of the estimated sample size.

7.4 Withdrawal criteria and loss to follow-up

In accordance with the current revision of the Declaration of Helsinki (Fortaleza, Brazil October 2013)[25] and with the applicable regulations, a participant has the right to withdraw from the study at any time and for any reason, without prejudice to the medical care provided by his doctor and /or referral centre in the future. A participant may be withdrawn from the study in the following scenarios:

- Participant withdraws consent.
- For safety reasons. In particular, subjects will be withdrawn from the study if any of the following occur:
    i. If adverse events (AEs) appear and, due to their type or severity, cause the participant not to remain in the study. See Appendix 2: Toxicity Management.
    ii. Pregnancy.
    iii. Subject is incorrectly included in the study based on exclusionary screening proviral DNA lamivudine resistance or any other protocol exclusion criteria.
    iv. Subject meets criteria for Confirmed Virologic Withdrawal or Precautionary Virologic Withdrawal.
        - Confirmed Virologic Withdrawal (CVW):
            - A VL≥ 50 copies/mL followed by a VL≥ 200 copies/mL in re-test 2-4 weeks apart.
        - Precautionary Virologic Withdrawal (PVW)

  - Three consecutive VL 50-200 copies/mL (each VL separated 2-4 weeks).
- At investigator discretion based on good clinical practice guidelines and clinical judgement deeming the participant ineligible to continue the study.
- Transfer to another hospital that is not a participating centre in the study.
- Loss to follow-up.
- The participant is not willing to comply with the procedures required in the protocol.

The causes leading to withdrawal from the study will be clearly recorded in the Clinical Research Document (CRD). A specific Withdrawal Visit will be scheduled to detail the participant's evolution, date of treatment discontinuation and new prescribed therapy (if applicable). If any ongoing AE is present at the time of Withdrawal Visit, the participant will be followed until its resolution or stabilization.

Participants discharged from the study will return to usual care according to the local guidelines and clinical practice.
Withdrawn participants may be replaced to achieve the estimated sample size, provided the stopping rule does not apply.

7.5. Security stop rules

Study will be terminated at any timepoint if two cases of CVW or PVW with development of INSTI resistance occur.

A security analysis will take place at week 24. Study will be prematurely discontinued if less than 80% participants in the per protocol population have VL<50 copies/mL (FDA-Snapshot algorithm).

7.6 Recruitment period

Study recruitment period is estimated in nine months, alternatively, until sample size is achieved.

A 60-day window is established between screening visit and day 1 visit.
If $CD4^+$ count or VL inclusion criteria are not met on first screening visit, one re-screening visit within 4 weeks would be allowed per participant. Re-screening visit will only be

performed if deemed appropriate by Medical Monitor and the investigator after detailed review of clinical history and mitigating factors.

8. STUDY TREATMENT

8.1 Study treatment

DTG/3TC (Dovato®).

8.2 Dosage

Dovato® (Dolutegravir 50 mg/Lamivudine 300 mg film-coated tablet):
Route of administration: oral.
Dose: Dolutegravir 50 mg/Lamivudine 300 mg/day.
Dosage: one 50 mg/300 mg film coated-tablet once daily.
Intervention: change of current antiretroviral treatment by DTG 50 mg/3TC 300 mg QD.

8.3. Packaging and labelling

Dovato® will be supplied by the hospital Pharmacy Department of each participating site for the treatment of their respective patients, dispensed in a controlled fashion and according to hospital directives.

The containers of Dovato® will be provided by the study Sponsor and the labelling for the study will be done by an outside agent in accordance with current national legislation.

8.4 Treatment compliance

Treatment adherence will be assessed by active questioning at study visit plus pill count, every visit from week 4 through week 96/end of study. Study drug will be labelled according to subject identification code, visit number and date. At every visit, the remaining medication will be returned by the participant to be counted and collected, and new medication will be assigned.

8.5 Other treatments permitted and prohibited

At study initiation, all concomitant medications will be recorded in the CRD and checked for potential drug-drug interactions at “https://www.hiv-druginteractions.org/checker".

Thereafter, all changes in medication will be detailed in the CRD. Additionally, all diagnostic, therapeutic or surgical procedures performed during the study period will be recorded, including date, indication, description of the procedure and clinical findings.

Prohibited drugs

The following medications or their equivalents can cause a decrease in the concentration of DTG and therefore should not be administered simultaneously with DTG.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampin or rifapentine
- St. John's wort

DTG/3TC is contraindicated with co-administration of medicinal products with narrow therapeutic windows, that are substrates of organic cation transporter (OCT2), including but not limited to fampridine (also known as dalfampridine). Co-administration has the potential to cause seizures due to increased fampridine plasma concentration.

NOTE: DTG should be administered 2 hours before or 6 hours after medicines with divalent cations (Ca^{++}, Fe^{++}), multiple vitamin supplements or antacids containing aluminium or magnesium salts.

All treatments considered experimental will be prohibited during the study.

9. STUDY DEVELOPMENT AND PROCEDURES

Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Week	**Screening**	**D1** (Basal visit)	**W4** (±2 days)	**W12** (± 4 days)	**W24** (± 6 days)	**W36** (±6 days)	**W48** (± 6 weeks)	**W72** (±8 days)	**W96** (±6 weeks)	**Follow up**
Informed Consent	x									
Inclusion and exclusion criteria	x	x								
Screening visit assessments	x									
Physical Exam†	x	x	x	x	x	x	x	x	x	
Vital signs and BMI	x	x	x	x	x	x	x	x	x	
Laboratory assessment (hemogram, chemistry including renal and hepatic function tests)	x	x	x	x	x	x	x	x	x	
Pregnancy test (if applicable), blood or urine	x	x	x	x	x	x	x	x	x	
Quantitative plasma HIV-1 RNA	x	x	x	x	x	x	x	x	x	
$CD4^+$ and $CD8^+$ count cells/µL	x	x	x	x	x	x	x	x	x	
PBMC proviral DNA RT Sanger sequencing	x									

PMBC Proviral DNA RT, PR and INSTI NGS	x								x	
Dispense study treatment		x	x	x	x	x	x	x		
Study treatment pill count			x	x	x	x	x	x	x	
Concomitant Medication review	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x

Table 1. Evaluation calendar per visit.

† Physical exam will be performed symptom-orientated from day 1 (V1) onwards.

A 60-day window is allowed between screening visit and day 1. Re-screening would only be allowed under special circumstances and careful evaluation by Medical Monitor and investigator (see section 7.6)

For the endpoint visits (week 48 and 96) a ±6-week window is allowed.

Withdrawal visit will be performed if any subject prematurely discontinues the study, see specific assessments in section 9.1

All serious adverse events will be reported from the moment the written informed consent is signed (see section 11 [Study safety]).

A Follow-up visit will be scheduled 28 days after the last dose of study medication to monitor and report any ongoing adverse event or laboratory abnormality considered to be potentially harmful for the participant.

9.1 Study visits and procedures

The study will be offered to participants that meet all the inclusion criteria and none of the exclusion criteria. There will be a total of 10 visits (screening, day 1, week 4, week 12, week 24, week 36, week 48, week 72, week 96 and a follow-up visit).

Screening visit:

Participants will receive the information relative to proceedings and study visits. If they agree to participate in the study, written informed consent should be signed before any procedure is performed. Screening assessments include:

- Review of inclusion and exclusion criteria.
- Demographic data: age, sex, race, country of origin
- HIV infection data: HIV subtype, mode of transmission, HIV + diagnosis date, nadir $CD4^+$, CDC stage, presence of previous AIDS diagnosis, HIV associated conditions, ART duration, time with VL <50 copies/ mL (excluding one blip [50-500 copies/mL preceded and followed by a VL<50 copies/mL] in the year prior to study entry) , previous antiretroviral treatments (number, type, reasons for change, date of change), resistance studies (resistance mutations detected in historical genotypic population studies, date of the genotypic study, viral load detected during the genotypic study).
- General medical history: previous illnesses, active diseases, active treatments, tobacco, alcohol and drug habits.
- Physical exam including weight, height, BMI, blood pressure and heart rate.
- Adverse events.
- Laboratory assessments will include:
    - Hemogram
    - Chemistry: liver function tests, renal function tests, fasting lipids, glucose.
    - Pregnancy test in women of childbearing potential (blood or urine

sample)

- AgHBs, antiHBc, antiHBs and HBV DNA in those with isolated antiHBc (if not performed in the 12 months prior to screening visit).
- $CD4^+$ and $CD8^+$ count.
- Viral load (quantitative plasma HIV-1 RNA)
- PBMC DNA Sanger sequencing (RT): using Big Dye Terminator (Applied Biosystem), and the Stanford HIVDB algorithm to interpret resistance mutations
- PBMC proviral DNA NGS sequencing (integrase, protease and RT) – sample will be saved to be performed retrospectively if participant continues to switch phase. For NGS, HIV-1 DNA will be extracted from PBMCs using the QIAamp® DNA blood minikit (Qiagen, Hiden, Germany) and a 3385 bp pol gene fragment will be amplified by nested PCR as described elsewhere[26]. NGS will be performed with Illumina in a Miseq instrument (Illumina, San Diego, CA, USA). Sequences wil be preprocessed with Prinseq-lite (http://prinseq.sourceforge.net/) and FLASH (http://www.cbcb.umd.edu/software/flash) programs[27,28]. The resulting aligned reads will be analyzed for HIV-1 drug resistance testing with PaSeq software (https://paseq.org/). The 1% threshold is for resistance interpretation. Baseline samples with 3TC or integrase resistance-associated mutations detected through NGS will undergo hypermutation analysis with Hypermut 2.0 software (https://www.hiv.lanl.gov/content/sequence/hypermut/hypermut.html).

Day 1:

- Review of inclusion and exclusion criteria.
- Concomitant medication.
- Adverse events.
- Physical exam including weight, height, BMI, blood pressure and heart rate.

- Switch to study treatment: DTG/3TC 50/300 mg once daily.
- Laboratory assessments will include:
    - Hemogram.
    - Chemistry: liver function tests, renal function tests, fasting lipids, glucose.
    - $CD4^+$ and $CD8^+$ count.
    - Viral load (quantitative plasma HIV-1 RNA).
    - Pregnancy test if women of childbearing potential (blood or urine sample)

Visits week 4 to week 96:

- Concomitant medication.
- Adverse events.
- Physical exam including weight, height, BMI, blood pressure and heart rate.
- The remaining study medication will be counted and collected, and new medication will be dispensed.
- Laboratory assessments will include:
    - Hemogram.
    - Chemistry: liver function tests, renal function tests, fasting lipids, glucose.
    - $CD4^+$ and $CD8^+$ count.
    - Viral load (quantitative plasma HIV-1 RNA).
    - Pregnancy test if women of childbearing potential (blood or urine sample).
- Week 96 additional assessments:
    - PBMC proviral DNA NGS sequencing (integrase, PR and RT)

In the event of a VL≥ 50 copies/mL at any time point between day 1 and week 96, a visit will be scheduled within 2-4 weeks to perform a VL re-test.

A Follow-up visit will be scheduled 28 days after the last dose of study medication to monitor and report any ongoing adverse event and concomitant medication or laboratory abnormality considered to be potentially harmful for the participant.

Investigators are allowed to perform additional assessments and procedures following local guidelines and clinical criteria (i.e vaccination, sexually transmitted infection screening), as long as they are not judged to interfere with study proceedings and are registered with detail in the medical history.

After week 96 study visit, the investigator is responsible for ensuring that the participants have continued access to antiretroviral treatment.

Withdrawal Study Visit:

If at any given point the participant is prematurely discontinued from the study, for any of the specified reasons in section 7.4 a Withdrawal Study Visit will be performed and registered in the CRD. This visit will include:

- Concomitant medication.
- Adverse events.
- Physical exam including weight, height, BMI, blood pressure and heart rate.
- Pregnancy test if women of childbearing potential (blood or urine sample).
- The remaining study medication will be counted and collected.
- Laboratory assessments will include:
    - Hemogram.
    - Chemistry: liver function tests, renal function tests, fasting lipids, glucose.
    - $CD4^+$ and $CD8^+$ count.
    - Viral load (quantitative plasma HIV-1 RNA).

- If CVW or PVW occur, resistance test (RNA Sanger sequencing, integrase, PR and RT, ViroSeq HIV-1 Genotyping System (Abbott Molecular, Spain) and PBMC proviral DNA NGS sequencing (integrase, PR and RT) will be performed.

9.2 Biological samples

All genotyping analysis will be centralized in 12 de Octubre University Hospital:

a. Proviral DNA population sequencing (Sanger, RT) and NGS (RT, PR, integrase)
    i. Sample: PBMC (10 mL blood, CPT tube).
    ii. Screening visit and also week 96 for NGS.

b. RNA population sequencing (Sanger, RT, PR, integrase) and PBMC proviral DNA NGS sequencing (integrase, PR and RT) in the event of CVW or PVW:
    i. Samples: Peripheral blood (10 mL blood, CPT tube) and PBMC (10 mL blood, EDTA tube).
    ii. Any timepoint throughout the study.

10. EVALUATION CRITERIA: STUDY VARIABLES

10.1 Primary endpoint

Proportion of virologic failure defined as HIV-1 RNA viral load ≥50 copies per mL at 48 weeks, ITT-e population, using the US Food and Drug Administration (FDA) snapshot algorithm).

ITT-e includes all participants receiving at least one dose of DTG/3TC.

10.2 Secondary endpoints

a. Proportion of VF (≥50 copies/mL) at week 96, ITT-e, FDA snapshot.
b. Proportion of VF (≥50 copies/mL) at week 48 and 96, per protocol population, FDA snapshot. Per protocol population excludes participants with protocol violations, lost to follow-up and those with low adherence (adherence at or below the 2.5th percentile of those in the study).
c. Proportion of VF (≥200 copies/mL) at week 48 and 96, ITT-e and PP population, FDA

snapshot.

d. Proportion of CVW at weeks 48 and 96, ITT-e and PP population, FDA snapshot.
e. Proportion of PVW at weeks 48 and 96, ITT-e and PP population, FDA snapshot.
f. Proportion of participants with VL<50 copies/mL week 48 and 96, ITT-e and PP, FDA snapshot.
g. Incidence of VF with drug resistance associated mutations.
h. Description of number and type of resistance-associated mutations in VF.
i. Analysis of factors associated to VF (i.e time to VF).
j. Proportion of VF in pre-specified subgroups:
   - Confirmed historical M184V/I vs No documented resistance mutations.
   - INSTI exposure vs No prior INSTI exposure.
   - Time virologically suppressed
   - Time on 3TC/FTC.
k. Proportion of participants with VF with baseline 3TC or INSTI resistance- associated mutations detected at baseline by NGS with 1, 5, and 20% threshold.
l. Proportion of participants with transient viral rebounds with baseline 3TC or INSTI resistance- associated mutations detected at baseline by NGS with 1, 5, and 20% threshold.
m. Type and frequency of resistance mutations (RT and integrase) in proviral DNA measured by NGS at baseline and week 96.
n. Change from Baseline in $CD4^+$ cell count and in $CD4^+/CD8^+$ cell counts ratio at weeks 48 and 96.
o. Incidence and severity of AEs and laboratory abnormalities through week 48 and 96.
p. Proportion of subjects who discontinue treatment due to AEs through weeks 48 and 96.
q. Descriptive demographic and clinical variables:

   - Demographic data: age, sex, race, country of origin
   - HIV infection data: HIV subtype, mode of transmission, HIV + diagnosis date, nadir $CD4^+$, CDC stage, presence of previous AIDS diagnosis, HIV associated conditions, ART duration, time with viral load <50 copies/mL (excluding one blip [50-500 copies/mL preceded and followed by a VL<50 copies/mL] in the year prior to study entry) , previous antiretroviral treatments (number, type, reasons

for change, date of change), resistance studies (resistance mutations detected in historical genotypic population studies, date of the genotypic study, viral load detected during the genotypic study, time since the virological failure or interruption of antiretroviral treatment and the completion of the genotypic study.

- General medical history: previous illnesses, active diseases, active treatments, tobacco, alcohol and drug habits.
- Physical exam including weight, height, BMI, blood pressure and heart rate.
- Laboratory assessment variables: Haemoglobin, leukocytes, lymphocytes, neutrophils, $CD4^+$ and $CD8^+$, GOT, GPT, GGT, Bilirubin, Creatinine, Ions, total cholesterol, HDL, LDL, triglycerides, glucose.

10.3 Bias control and limitations

The absence of 3TC resistance mutations in the population genotype of proviral DNA Sanger does not guarantee the success of DTG/3TC treatment. However, based on the results from our pilot study ART-PRO[29], we believe that this is a reasonable working hypothesis. If any case of VF occurred, proviral DNA RT+ INSTI NGS for retrospective analysis will allow to detect if any archived resistance minority variants were present at baseline and could therefore be the cause of failure.

Proviral HIV analysis could be limited by the number of latently infected CD4 lymphocytes present in the sample, so PBMCs will be used to ensure maximum resistance detection capacity.

Objective primary and secondary endpoints will allow to reduce the potential bias associated with the open label design of the study.

11 STUDY SAFETY

11.1 Drug safety reference information

In this study, the reference safety information will be the European Medicine Agency Dovato® product information[30].

11.2 Definitions

Adverse event (AE):

Any medical event presented by a clinical research subject to whom a pharmaceutical product has been administered and does not necessarily have to have a causal relationship with said treatment.

The following will be registered as an AE:

- Significant or unexpected worsening of the condition to be treated during the study.
- Exacerbation of pre-existing chronic, intermittent or episodic diseases, including an increase in frequency and /or severity.
- A new condition detected or diagnosed after the administration of the product under investigation, even if it could have been present before study initiation.
- Suspicious clinical signs, symptoms or sequelae.
- Clinical signs, symptoms or sequelae of a suspected overdose of the medicinal product under investigation or concomitant medication.
- Obvious failure of the expected biological or pharmacological effect.
- Any medical reaction before, during or after the treatment resulting from the procedures specified in the protocol, such as those derived from sampling.
- Grade III-IV laboratory events, as classified by DAIDS toxicity scales[31].

It will not be considered, and therefore not recorded as an AE:

- Medical or surgical procedures due to the course of the disease allowed in the clinical study.
- Situations leading to hospital admission for social or convenience reasons,

without any medical underlying reasons.

- Clinical signs, symptoms or sequelae of the study disease or its expected progression.

Serious adverse event (SAE):

Any medical event leading to:

- Death
- Life endangerment
- Hospital admission, prolongation of existing hospital admission
- Persisting or significant disability / incapacity, or results in a congenital anomaly or defect.
- All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5 (if INR measured) which may indicate severe liver injury must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis).
- Events not included in the preceding paragraphs but that may endanger the participant or require intervention to prevent any of the abovementioned results. Examples of such events are intensive treatment in an emergency department or at home for an allergic bronchospasm; blood dyscrasias or seizures that do not lead to hospital admission, or the development of dependence or drug abuse.

For notification purposes, suspicions of AEs that are considered medically important will be treated as serious, even if they do not meet the above criteria, such as those that put the participant at risk or require intervention to prevent any of the abovementioned outcomes.

Unexpected Serious Adverse Reaction (SUSAR):

Any serious adverse event which nature, severity or consequences are not consistent with the available product information.

11.3 Casualty evaluation

Investigators will assess casualty of the AE with the study medication according to the following definitions:

Relatedness Rating	Definition
Related	An adverse event in which there is a reasonable possibility of a causal relationship to the use of the study drug. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g. a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.
Not Related	An adverse event which is not related to the use of the drug.

11.4 Intensity evaluation

The intensity of the AE will be graded following the DAIDS grading table for Severity of AEs[31].

11.5 Safety variables and parameters

To investigate AEs, investigators will enquiry at every visit for AEs. To avoid bias and to promote spontaneous report of AEs, questions addressed to participants will be open and are not to have a leading nature. Questions may be as:

- How are you?
- Have you presented any symptoms since the last visit?
- Have you needed evaluation by another healthcare professional?
- Have you visited any emergency department?
- Have you taken any other medications besides antiretroviral treatment since the last visit? If so, why?

11.6 Adverse events information

All SAEs and AEs will be collected from the signing of the ICF until the follow-up visit.

All AEs occurring during the study, until the end of the follow-up period, whether or not they are attributed to the study medication, will be evaluated by the investigator and recorded in detail in the CRD. Data on the description of the AE, start and end date, severity/intensity, causality with the investigational drug product, evolution, outcome of the AE and measures adopted (treatments, additional complementary examinations) will be recorded, including those related to the investigational medication (eg, suspension). Regardless of the causal relationship with the study drug, all AE will be followed until resolution or until considered stable. The investigator is authorized to judge if the severity of the AE requires discontinuation of the treatment or participant withdrawal from the study. Participants may also voluntarily withdraw if they perceive an AE as not tolerable. A Follow-up visit will be scheduled 28 days after the last dose of study medication to monitor and report any ongoing adverse event or laboratory abnormality considered to be potentially harmful for the participant.

The outcome of the AE will be evaluated as follows:
- Resolved.
- Improved
- Unchanged.
- Worsening.
- Death.

Action taken by the investigators with regards to the study medication:
- None.
- Discontinuation.
- Interruption.
- Dose reduction.
- Delay in the beginning of treatment.

11.7 Pregnancy

Female participants will be instructed to notify the investigator if they become pregnant at any time during the study.

Women of childbearing potential should be informed about the potential risk of neural tube disorders with DTG (see Appendix 1). These defects happen early in pregnancy, before women may know they are pregnant.

Women of childbearing age should use an appropriate contraceptive method for the duration of the study and up to 4 weeks after completion (see Appendix 1, Guidance on Pregnancy and Breast Feeding). The chosen contraceptive method will be documented in the subject's medical records. Women of childbearing potential will be informed of the potential risk of neural tube defects and will be counselled on avoiding pregnancy, safer sexual practices and the proper use of their chosen contraceptive methods.

A pregnancy test (blood or urine) will be performed at every study visit. Any pregnancy occuring within the study will result in immediate withdrawal from the study and discontinuation of study drug treatment.

Each pregnancy will be notified to the Medical Monitor as soon as it is known to the investigator. Information will be recorded on the appropriate form (see Appendix 5 and 6) and submitted to the Sponsor within 24 hours of of learning of a subject's pregnancy. All pregnancies should also be reported to ViiV Healthcare within 1 week, regardless of causality. Additionaly, pregnancies will be registered in the AntiretroviralPregnancy Registry (www.apregistry.com).

Pregnancy should be followed to determine the outcome, including spontaneous or voluntary termination, birth details, and the presence or absence of any defect such as congenital anomaly or complications for the mother and / or newborn. Pregnancy results should also be recorded for female partners of a male participant who is participating in the study. If the outcome of pregnancy meets SAE criteria or if the newborn has a SAE, the procedures described for the notification of SAE will be followed. Spontaneus abortions must be reported as a SAE.

11.8 Notification procedure of SAEs

Investigators should notify the sponsor or whoever assumes the tasks delegated by the sponsor within a maximum period of 24 hours after learning of the existence of a SAE, with an accompanying SAE notification form.

The investigator shall complete and sign the SAE report form (Appendix 6) and send it by fax:

915542283
Fundación SEIMC-GESIDA
C/ Agustín de Betancourt nº 13, entreplanta
Madrid 28003

and/or email to: **pharmacovigilance@f-sg.org**

SAEs associated with DTG/3TC should also be reported to ViiV Healthcare within 24 hours, regardless of casualty. The sponsor or whoever assumes the tasks delegated by the sponsor may request additional information from the investigator. The investigator will provide information to the sponsor or to those who assume the tasks delegated by the sponsor whenever requested and, in any case, when their initial evaluation changes in terms of severity or causality. The sponsor or whoever assumes the tasks delegated by the sponsor will keep a detailed record of all the SAEs communicated to them by the researchers.

11.9 Notification procedure of severe and unexpected adverse events (SUSAR)

The sponsor or whoever assumes the tasks delegated by the sponsor, will notify all the suspicions of SUSAR according to the current regulations on clinical trials to the Spanish Agency of Medicine and Health Products (AEMPS), to the ethical committees (CEIC) and to the authorities of the Autonomous Community of Madrid within a maximum period of fifteen calendar days from the moment they are aware of their existence. When the SUSAR has caused the death of the participant or endangered his life, the notification will be made within a maximum period of seven calendar days from the moment in which it is known. The relevant information regarding subsequent events will be supplemented within eight days.

The minimum initial information for the notification of an adverse event must include the following:

- Adverse event and starting date.
- Initials, sex and age (or date of birth) of the participant.
- Information about the treatment received.

- Name and address of the doctor notifying the AE.

- Causality relationship with the medication under study.

12 ETHICAL ISSUES

12.1 General and particular rules for investigators

Investigators will strictly adhere to the provisions of this protocol, fully completing the data collection notebook sheets.

The study will follow the prevailing recommendations for medical research involving human subjects, as reflected in the latest version of the Declaration of Helsinki and the current the applicable Spanish Legislation on Clinical Studies (RD 1090/2015, of December 4, which regulates clinical trials with medications).

12.2 Informed consent

All participants will be informed before starting the study of the objectives, procedures, potential related inconveniences derived from said procedures, and the risks of the study. All subjects will receive a participant information sheet, along with the written informed consent that must be signed at screening visit before any procedure relating to the study is performed.

12.3 Safety and confidentiality procedures

All information obtained from this study is considered confidential. The confidentiality of the personal and genetic data obtained will be protected, respecting at all times the basic ethical principles of research with biological samples, and as established by the applicable legislation (Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data).

Participants may at any time exercise their right to access and modify their information, as established by the Spanish Organic Law for Personal Data Protection 3/2018 and the European General Data Protection Regulation 2016/679.

In case of considering the participation in a new study, with a different objective to that indicated in the information sheet, the participant will be informed and new consent and permission to use the samples will be requested. Biological samples will not be used for other studies without the explicit permission of the participant and the approval of the CEIC.

12.4 Insurance

There will be civil liability insurance policy for the trial as established in article 8 of RD 1090/2015, of December 4.

13 PRACTICAL CONSIDERATIONS

13.1 Responsibilities of participants in the study

Rules for participants

Participating subjects must follow the indications of the investigators and communicate any eventuality to them.

Participants will be duly informed of the prohibitions or restrictions to which they must be adherent throughout the study. Failure to comply with these recommendations will imply abandoning the study.

All subjects participating in the study have the right to leave the study at any time, withdrawing their consent, without having to justify this decision and without causing any detriment effect in their clinical follow-up. If this occurs, the investigator will try to ensure that the subject performs all the necessary evaluations to ensure that no adverse events occur and to ensure appropriate follow-up.

Rules for investigators

Investigators are obliged to comply with the norms established in the current legislation regarding clinical trials.

Protocol compliance

Protocol deviations should be avoided. If these occur, the investigator must inform the

monitor and the implications of such deviations will be reviewed and discussed among the investigation team. Deviations from the protocol will be documented specifying the reasons, date, action taken, and the impact on the participant and the trial. Documentation regarding deviations from the protocol will be stored in the Investigator's Archive.

13.2 Monitoring, auditing and inspection

The study will be monitored by a monitor of SEIMC-GESIDA Foundation, who will prepare an appropriate monitoring plan for the study. Regular visits and phone calls will be made to investigators. During visits, the monitor should review participant and study drug records and documents, and the preservation of said documents. In addition, the monitor should evaluate the study procedures and discuss any problems with the investigator. During the course of the study, audit visits may be carried out in the participating centres. The investigators will allow direct access to the source data / documents for monitoring, auditing or review by the La Paz Research Ethics Commitee (Comité Ético de Investigación Clínica, CEIC) and inspection by the Health Authorities.

13.3 Study documentation

All documentation related to the study (protocol, CRD, informed consent, authorizations...) will be archived during the study in a safe place and easily accessible by the research team. All information contained in clinical, histological, biochemical and molecular reports, observations or other activities are necessary for the reconstruction and evaluation of the study. Examples of these documents are hospital records, laboratory notes, memorandums, participant diary, evaluation checklists, medication dispensing record or other pharmacy documents, recording of data obtained from automated devices, digitized photo files, X-rays, etc.

13.4 Data management

Processing, communication and transfer of personal data of all participating subjects will comply with the provisions of Organic Law 03/2018, on the protection of personal data. At the time of registration, a Participant Number will be assigned to each participant. This information will be registered in the CRD. The investigator will be responsible for keeping the appropriate information about each participant so that health authorities can have

access to such information if necessary. These records must be kept confidential for the period of time legally mandated by current regulations.

13.5 Publication conditions

All information from the study will be considered confidential. The Principal Investigator assumes the set of responsibilities linked to this function, and the exclusive ownership of the results of the study, which may be freely exploited. Principal Investigator commits to publish the results of the study in a scientific journal or to make them available to the public as established by the Declaration of Helsinki, item 36: “Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication”.

13.6 Procedure for the modifications of the protocol

Any protocol modifications must be documented with a protocol amendment. Amendments will be duly identified by their chronological order number, dated and signed by the sponsor and the investigator. If the modifications are relevant, the sponsor must request authorization from the Reference CEIC and the AEMPS, as established by current regulations.

13.7 Ethics committee of research with medicines (CEIC)

The protocol and the informed consent documents will be evaluated by the CEIC of La Paz University Hospital whose composition is already known and accredited by the health authorities of the Autonomous Community of Madrid (http://www.msssi.gob.es/profesionales/ pharmacy / ceic / pdf / ceicsacreditadoses.pdf). The decision of the CEIC regarding the development of the study will be provided in writing to the investigator. A copy of that decision must be sent to the sponsor.

The sponsor will present the required progress reports of the study to the CEIC and will communicate the suspicions of serious and unexpected adverse reactions. Upon completion of the study, the sponsor must inform the CEIC.

14 STATISTICAL ANALYSIS

14.1 Sample size estimation

In previous studies of switch to DTG/3TC the rate of virologic failure at week 48 has been 0.7%[24]. With 120 participants recruited, and considering the same proportion of virologic failures, we could discard differences in the proportion of virologic failures >4% with a binomial estimation of the 95 confidence interval.

14.2 Statistical analysis

In addition to main analysis, a security analysis will take place at week 24, to determine if study is to be continued (section 7.5).

To compare two means we will use Student's t test (if normal distribution) or non-parametric Wilcoxon rank-sum (Mann-Whitney) test. If needed, an adjusted analysis would be performed. Proportions will be compared with x2 test.

Endpoints will be analysed including the intention-to-treat exposed population, that is, all participants who received at least one dose study drug.

Main Analysis – Primary endpoint:

The main primary endpoint will be the proportion of virological failure HIV-1 RNA VL≥50 copies/mL, at 48 weeks, following FDA snapshot algorithm in the population "by intention to treat -exposed". This result will be expressed as a percentage and 95% confidence interval.

Secondary planned analysis -Secondary endpoints:

a. Proportion of VF (≥50 copies/mL) at week 96, ITT-e, FDA snapshot. This result will be expressed as a percentage and 95% confidence interval.
b. Proportion of VF (≥50 copies/mL) at week 48 and 96, PP population, FDA snapshot.
c. Proportion of VF (≥200 copies/mL) at week 48 and 96, ITT-e and PP population, FDA snapshot. This result will be expressed as a percentage and 95% confidence interval.

d. Proportion of CVW at weeks 48 and 96, ITT-e and PP population, FDA snapshot. This result will be expressed as a percentage and 95% confidence interval.
e. Proportion of PVW at weeks 48 and 96 ITT-e and PP population, FDA snapshot. This result will be expressed as a percentage and 95% confidence interval.
f. Proportion of participants with VL<50 copies/mL week 48 and 96, ITT-e and PP population, FDA snapshot. This result will be expressed as a percentage and 95% confidence interval.
g. Incidence of VF with drug resistance associated mutations. Descriptive analysis of number and type of resistance mutations.
h. Univariant and multivariant logistic regression analysis of factors associated to virological failure (time to VF).
i. Proportion of VF in pre-specified subgroups:
   - Confirmed historical M184V/I vs No resistance mutations.
   - INSTI exposure vs No prior INSTI exposure.
   - Time virologically suppressed.
   - Time on 3TC/FTC.
j. Proportion of participants with VF with baseline 3TC or INSTI resistance- associated mutations detected at baseline by NGS with 1, 5, and 20% threshold.
k. Proportion of participants with transient viral rebounds with baseline 3TC or INSTI resistance- associated mutations detected at baseline by NGS with 1, 5, and 20% threshold.
l. Univariant and multivariant logistic regression model analysis of the association between 3TC or integrase resistance-associated mutations by NGS and potentially confounding variables reaching signification below 0.1 in the different univariant models.
m. Logistic regression model analysis of the impact in virological response of mutations detected by NGS.
n. Type and frequency of resistance mutations (RT and integrase) in proviral DNA by NGS at baseline and week 96. Hypermutation analysis of mutations detected through NGS.
o. Univariant and multivariant logistic regression analysis of factors associated to change on frequency of resistance mutations detected by NGS at baseline and week 96.

p. Incidence and severity of AEs and laboratory abnormalities grade III-IV through week 48 and 96.

q. Proportion of subjects who discontinue treatment due to AEs through weeks 48 and 96.

r. Change from Baseline in $CD4^+$ cell count (W48 minus baseline and W96 minus W48) and in $CD4^+/CD8^+$ cell counts ratio at weeks 48 and 96.

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APPENDIX 1. GUIDANCE ON PREGNANCY AND BREAST FEEDING

Preliminary results from an observational study revealed an increased risk **of neural tube defects in infants born to women who took dolutegravir** at the time of conception. Later data from the study has shown a numerically higher rate of neural tube defects with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. A causal relationship of these events to the use of dolutegravir has not been established. No increased risk was reported in infants born to women who started dolutegravir later during pregnancy.

Reproductive toxicology studies have not shown any relevant findings. Likewise, other data on the use of dolutegravir in pregnancy, including data from the Antiretroviral Pregnancy Registry (APR), clinical trials and post-marketing use have not indicated an increased risk of neural tube defects, although the extent of exposure from these other data sources is currently insufficient to confirm or rule out an increased risk of neural tube defects with DTG-containing regimens taken at the time of conception and in early pregnancy.

Further information about this potential risk is provided in the Investigator Brochure for DTG-containing products and, where applicable, the approved Local Prescribing Information).
Reproductive toxicity data for 3TC and DTG guidance on the use of these active principle in pregnancy, is given in the relevant approved Local Prescribing Information.

A female, may be eligible to enter and participate in the study if she:

a. is of non-child-bearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or,
b. is of child-bearing potential with a negative pregnancy test at both Screening and Visit 1 and agrees to use one of the highly effective methods to avoid pregnancy documented below.

Women of childbearing potential should be informed about the potential risk of neural tube disorders with DTG. These defects happen early in pregnancy, before many women even know they are pregnant.

Women of childbearing potential should be counselled about the importance of pregnancy avoidance, safer sexual practices and adherence to contraception requirements throughout the study, and for at least 4 weeks after the last study visit.

Women of childbearing potential must be using a highly effective method of contraception as detailed below, which should be documented in the eCRF.

Females of childbearing potential should be reminded about the importance of pregnancy avoidance and of adherence to contraception requirements at every study visit.

If pregnancy is confirmed while taking DTG/3TC, treatment should be discontinued and the subject should be switched to an alternative regimen

Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive potential:

- Complete abstinence from penile-vaginal intercourse from 2 weeks prior to administration of Investigational Product, throughout the study, and for at least 4 weeks after discontinuation of all study medications;
- Any intrauterine device with published data showing that the expected failure rate is <1% per year:

Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
bilateral tubal occlusion.

- Male partner sterilization confirmed prior to the female subject's entry into the study, and this male is the sole partner for that subject;
- Approved hormonal contraception:

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral intravaginal or transdermal.

Progestogen-only hormonal contraception associated with inhibition of ovulation: injectable.

- Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently, in accordance with the approved product label and for at least 4 weeks after discontinuation of study medication.

Reporting of pregnancy information

Any pregnancy that occurs during study participation must be reported (see Appendix 5 and 6). To ensure subject safety, each pregnancy must be reported to Sponsor within 24 hours of learning of its occurrence. All pregnancies should also be reported to ViiV Healthcare within 1 week, regardless of causality. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to Sponsor. Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event or serious adverse event. Spontaneous abortions must be reported as a serious adverse event.

Any serious adverse event occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Sponsor.

Investigators are also encouraged to report any pregnancy that occurs during study participation to the Antiretroviral Pregnancy Registry (APR) prospectively, and before the pregnancy outcome. More information including copies of applicable case report forms and fax numbers are available at www.apregistry.com.

APPENDIX 2: RISK ASSESSMENT AND TOXICITY MANAGEMENT

Reference safety information for this study is the Investigator Brochure and/or approved Local Prescribing Information for the study treatments.

Here we summarized some risk and toxicity information, especially of DTG.

The current key risks associated with the use of the DTG single entity or other DTG-containing products are presented below. Further information on these, and other known or theoretical risks associated with the use of these products, is included in the Investigator Brochure for the DTG-containing products, and, where applicable, in the approved Local Prescribing Information.

Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: dolutegravir/lamivudine Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information		
Hypersensitivity and rash	Hypersensitivity reactions has been observed uncommonly with DTG. Rash, generally mild to moderate in intensity, was commonly reported in DTG Phase IIb/III clinical trials. No episodes of severe rash, such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme, were reported.	Subjects with history or presence of allergy to any of the study drugs or their components are excluded. Specific/detailed toxicity management guidance is provided for hypersensitivity reactions and rash. The subject informed consent form includes information on this risk and the actions subjects should take in the event of a hypersensitivity reaction or associated signs and symptoms.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: dolutegravir/lamivudine Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information		
Drug induced liver injury and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for antiretroviral therapy containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus and/or hepatitis C virus co-infection, improvements in immunosuppression because of human immunodeficiency virus (HIV) virologic and immunologic responses to DTG-containing antiretroviral therapy, along with inadequate therapy for hepatitis B virus co-infected subjects, likely contributed to significant elevations in liver chemistries. There have been rare post-marketing reports of acute hepatic failure in association with DTG-containing regimens. Current treatment guidelines do not recommend mono-therapy with 3TC for patients with hepatitis B virus infection, which is what subjects on DTG/3TC would be receiving. Emergence of HBV variants	Subjects meeting any of the following criteria during the screening period are excluded from participating • Alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (ULN) or ALT ≥ 3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) • Unstable liver disease, cirrhosis and/or known biliary abnormalities (except for hyperbilirubinemia or jaundice due to Gilbert's syndrome or asymptomatic gallstones) • Subjects with an anticipated need for hepatitis C virus therapy with interferon and/or ribavirin prior to the primary endpoint • Positive Surface Hepatitis B Ag (HBAgS) OR negative HBAgS and negative hepatitis B surface antibody (anti-HBs) with positive anti-core antibody (anti-HBc) and positive HBV DNA. • Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected drug induced liver injury or other clinically significant liver chemistry elevations

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: dolutegravir/lamivudine Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information		
	associated with resistance to 3TC has been reported in HIV-1-infected patients who have received 3TC-containing antiretroviral regimens in the presence of concurrent infection with HBV. Additionally, discontinuation of 3TC in hepatitis B virus infected subjects can result in severe exacerbations of hepatitis B virus. For subjects co-infected with hepatitis C virus and HIV, [some] treatment guidelines recommend that the hepatitis C virus infection is treated first before starting treatment for the HIV. Additionally, interferon and/or ribavirin toxicity maybe frequent and difficult to differentiate causality from investigational product.	
Theoretical serious drug interaction with dofetilide and pilsicainide	Dolutegravir must not be administered concurrently with medicinal products with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to dofetilide, pilsicainide or fampridine (also known as dalfampridine.	The co-administration of DTG/3TC with dofetilide or fampridine are prohibited in the study.
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviours are	Due to the elevated risk in the HIV-infected population,

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: dolutegravir/lamivudine Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information		
	common in HIV-infected patients. In clinical trials, the psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was generally similar or favourable compared with other antiretroviral therapy, although a higher incidence of depression and suicidal ideation /behaviours with DTG compared with darunavir/ritonavir was noted in the FLAMINGO clinical study. An evaluation of aggregate data, including post-marketing data concluded that a causal association between DTG and depression and suicidal behaviours could not be ruled out. These events occur primarily in patients with a prior history of psychiatric illness. The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared to efavirenz/tenofovir/emtricitabine in the SINGLE clinical study; however, this was not duplicated in other VH Sponsored Phase IIb/III studies with DTG or DTG/ABC/3TC.	treatment emergent assessment of suicidality will be monitored during this study. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: dolutegravir/lamivudine Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information		
Renal function	Lamivudine is eliminated by renal excretion and exposure increases in patients with renal dysfunction.	Due to requirements for dose reduction of 3TC in patients with renal dysfunction, subjects with a creatinine clearance <30 mL/min (CKD-EPI method) are excluded. Participants who develop a Grade 4 eGFR toxicity (per DAIDs criteria) should have study drug withdrawn.
Neural tube defects	In a birth surveillance study conducted in Botswana (the Tsepamo study), preliminary results showed that in babies born to women who were taking DTG when they became pregnant there was an increased risk of neural tube defects compared with the background rate. Later data from the study has shown a numerically higher rate of neural tube defects with exposure to DTG compared to non-DTG-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. A causal relationship of these events to the use of DTG has not been established. No increased risk of these defects was reported in babies born to mothers	Pregnancy testing should be performed before initiation of DTG therapy in all women of childbearing potential (negative pregnancy test at screening and randomization). (Section 9) Women who are pregnant or who plan to become pregnant, are excluded. All women of reproductive potential should use a highly effective method of contraception – see Section11.7 /Appendix 1 Subject informed consent form provides information about this potential risk.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: dolutegravir/lamivudine Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information		
	who started DTG containing regimen later in pregnancy Dolutegravir was tested in a complete package of reproductive toxicology studies, including embryofoetal development studies. No adverse development outcomes, including neural tube defects, were identified. In reproductive toxicity studies in animals, DTG was shown to cross the placenta. Data analysed to date from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with DTG.	

Toxicity Management

In the event of a discontinuation of a DTG-containing product for suspected drug induced liver injury, other clinically significant liver chemistry elevations, severe skin reaction or hypersensitivity reaction, subjects should not be rechallenged with a DTG-containing product due to the risk of a recurrent reaction. These subjects should be withdrawn from study and seek/be reviewed for alternative antiretroviral therapy (but may continue on study, but off study drug). Further details on this are provided in this section as appropriate.

- **<u>Hypersensitivity and rash</u>**

Allergic Reaction

Subjects may continue investigational product(s) for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the investigational product(s) should permanently discontinue the investigational product regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the adverse event.

Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing antiretroviral therapy. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. The index case of a hypersensitivity reaction with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme have been reported for DTG in clinical trials.

Subjects with an isolated Grade 1 rash may continue investigational product at the Investigator's discretion. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Subjects may continue investigational product for an isolated Grade 2 rash. However, investigational product (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Subjects should permanently discontinue investigational product (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the adverse event.

The rash and any associated symptoms should be reported as adverse events (see (Section 11) and appropriate toxicity ratings should be used to grade the events (based on DAIDS [Division of ADS] toxicity gradings).
If the etiology of the rash can be diagnosed as being unrelated to investigational product and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

- **Liver Chemistry Stopping and Follow up Criteria**

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study drug and the follow-up period (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

For any participant meeting one of the criteria outlined in Table 1 or Table 2, or if the Investigator believes that it is in the best interest of the patients, the Investigator must follow the required actions and follow up assessments also outlined in these tables.

Table 1 Liver Chemistry Stopping Criteria - Liver Stopping Event

ALT absolute	ALT ≥ 8xULN
ALT increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** International normalised ratio (INR)>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks

	(See Table 2 for actions where subjects CAN be monitored weekly for >2 weeks)
Symptomatic[3]	ALT ≥ 3xULN (if baseline ALT is ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity ALT ≥ 3x baseline (if baseline ALT>ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event

Actions	***Follow Up Assessments***

• Immediately hold DTG.
• If a causal relationship between the liver event and DTG cannot be ruled out, then DTG must be permanently discontinued and the Subject not rechallenged due to the risk of a recurrent reaction.
• Report the event to the Sponsor by telephone within 24 hours.
• Events of possible drug-induced liver injury with hyperbilirubinemia[2] will be reported to Sponsor as serious adverse events using the serious adverse event case report form.
• Complete the liver event case report form for all events meeting liver stopping criteria, and submit to Sponsor within one week of first becoming aware of the event
• Perform liver event follow up assessments.
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below).
• If the liver event has a clear underlying alternative cause, other than drug-induced liver injury, then Drug Restart may be considered by Sponsor (for exception see Liver Safety – Study Treatment Rechallenge and Restart)
• If restart is not allowed or not granted, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments.
MONITORING:
• Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries (include ALT,
	• Viral hepatitis serology, including:
	  • Hepatitis A immunoglobulin M (IgM) antibody;
	  • HBsAg and hepatitis B core antibody;
	  • Hepatitis C RNA;
	  • Hepatitis E IgM antibody.
	• Cytomegalovirus IgM antibody.
	• Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
	• Syphilis screening.
	• Drugs of abuse screen, including alcohol. Record alcohol use on the liver event case report form
	• Serum acetaminophen adduct High Performance Liquid Chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week (2) [FDA, 2009]). The site must contact the medical monitor when this test is required. NOTE: not required in China
	• Serum creatinine kinase and lactate dehydrogenase.
	• Fractionate bilirubin, if total bilirubin ≥1.5xULN.
	• Obtain complete blood count with differential to assess eosinophilia.

aspartate aminotransferase, alkaline phosphatase, bilirubin) and perform liver event follow up assessments at the central laboratory as described to the right. • A specialist or hepatology consultation is recommended. • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline.	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Complete Liver Imaging and/or Liver Biopsy case report form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **or** ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury **must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia). Record the appearance or worsening of any such clinical symptoms on the adverse event report form.

Table 2 Liver Chemistry Increased Monitoring Criteria

Criteria	Actions
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for >2 weeks.	• Notify the medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) until resolution, stabilisation (ALT <5×ULN on 2 consecutive evaluations) or return to within baseline

	• If at any time subject meets the liver chemistry stopping criteria, proceed as described above

Liver Safety – Study Treatment Rechallenge and Restart

Rechallenge refers to resuming study treatment following drug induced liver injury. Following DILI, drug rechallenge is associated with a 13% mortality across all drugs in prospective studies (1) [Andrade et, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.
In the event of a discontinuation of DTG/3TC for a Liver Stopping Event, subjects should not be rechallenged with DTG/3TC due to the risks associated with rechallenge.

'Drug restart' refers to resuming study treatment following a Liver Stopping Event in which there is a clear underlying cause (other than drug induced liver injury) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis).
If a causal relationship between the liver event and DTG/3TC cannot be ruled out, then DTG/3TC must be permanently discontinued and the subject not rechallenged.
Drug restart with DTG/3TC in a patient who has a Liver Stopping Event is permitted providing the investigator follows the specific Drug Restart Criteria:

Drug Restart Following Transient Resolving Liver Events Not Related to Study Drug

Restart can be considered when liver chemistries improve to within 1.5x baseline and ALT<3xULN) where:

- Liver chemistries have a clear underlying cause other than drug-induced liver injury (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury.
- The subject is receiving compelling benefit and benefit of drug restart exceeds risk
- Approval from Study Team and Ethics Committee or Institutional Review Board for the drug restart has been obtained.

- The subject has been provided with a clear description of the possible benefits and risks of drug restart, including the possibility of recurrent, more severe liver injury or death.
- The subject has also provided signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study file.
- Following drug restart, the Subject will return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

See Appendix 3. Liver safety -Checklist for Drug Restart Approval or Refusal.

Suicidal Risk Monitoring

Subjects with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor subjects for suicidality before and during treatment.

Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour, or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour.

If any subject experiences a possible suicidality-related adverse event (PSRAE) while participating in this study that is considered by the Investigator to meet ICH E2A (ICH E2A, 1994) definitions for seriousness, the Investigator will collect information using a PSRAE case report form (or agreed alternative) in addition to reporting the event on a serious adverse event case report form. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-

related. PSRAE forms should be completed and reported to Sponsor within one week of the investigator diagnosing a possible suicidality-related serious adverse event.

Decline in Renal Function

Treatment with DTG/3TC must be discontinued in any Subject developing a grade 4 decreased in creatinine clearance.

A confirmatory creatinine clearance assessment should be conducted within 2 weeks.

References:

1. Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

2. FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Accessed 07 January 2015 at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022145s032,203045s010,205786s001lbl.pdf

3. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Clinical safety data management: Definitions and standards for expedited reporting. ICH E2A. 1994

APPENDIX 3: Liver Safety – Checklist for Drug Restart Approval or Refusal

"Drug restart" after discontinuation of Study Drug due to Liver Stopping Criteria (as defined in the protocol), can only be approved by the Study's Governing Body (e.g., Protocol/Study Team or Study Chair) or Principal Investigator for **transient, defined non-drug-induced liver injury with no evidence of:**

- immunoallergic injury/HLA association with injury
- drug-induced liver injury
- alcoholic hepatitis

Investigators MUST:

1. Hold study drug while labs and evaluations are completed to assess diagnosis, and not restart until "Drug restart" has been approved by the Study's Governing Body or Principal Investigator.
2. Complete the table below and submit to the Study's Governing Body or Principal Investigator. The Liver Event case report form should already have been submitted to the Study's Governing Body or Principal Investigator, along with liver imaging and/or liver biopsy case report forms and/or SAE case report form where applicable. Where restart of TRIUMEQ or any other ABC-containing product is being considered, provide documentation verifying HLA-B*5701 status.

Subject Number:	**Yes**	**No**
Have liver chemistries improved to within 1.5x baseline and ALT<3xULN?		
Was subject's HIV infection stable or improving on Study Drug?		
Were any of the **following high risk factors** included in the initial liver injury event? **(Do not restart if 'Yes' for any one of the following high risk factors)**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (aspartate aminotransferase>ALT, typically <10xULN)		
• Study Drug (other than ABC) has an HLA genetic marker associated with liver injury		
For restart of TRIUMEQ, or any other abacavir- containing Study Drug, the subject MUST be HLA-B*5701 negative[1] Specify HLA-B*5701 status[2]:		

1. In countries/regions where HLA-B*5701 pre-therapy screening is not considered standard of care, subjects stopping abacavir- containing study drug due to Liver Stopping Criteria MUST be tested and found to be negative for the HLA-B*5701 allele before abacavir- containing Study Drug can be re-started.
2. If study drug does not containing ABC then record HLA-B*5701 status as "not applicable"

APPENDIX 4: SERIOUS ADVERSE EVENT REPORT FORM

SERIOUS ADVERSE EVENT REPORT FORM
SEIMC-GESIDA Foundation

Principal Investigator: **Site:** **Phone:** **Country:**	**PROTOCOL CODE** (sponsor)..... **EUDRACT N°/ Protocol N°** AEMPS.....	☐ Initial Report ☐ Follow up Report
NOTIFICATION N° (to be completed by sponsor):		

I. INFORMATION ABOUT THE ADVERSE EVENT

PATIENT CODE:	DATE OF BIRTH (dd/mm/yyyy):	AGE (Years):	☐ MALE ☐ FEMALE	WEIGHT (Kg):	HEIGHT (cm):	SAE START DATE (dd/mm/yyyy):	SAE START TIME (hh:mm):

SERIOUS ADVERSE EVENT:	Detail the symptoms if there is no diagnosis:
DATE OF KNOWLEDGE OF SERIOUS ADVERSE EVENT (DD/MM/YYYY):	
DESCRIPTION OF THE SERIOUS ADVERSE EVENT (Including relevant exploration, laboratory results, course of the event, etc)	
HAS A LACK OF QUALITY BEEN DETECTED IN THE SUSPECTED PRODUCT? ☐ YES ☐ NO	
IS IT A SUSPECTED TRANSMISSION OF AN INFECTIOUS AGENT THROUGH A MEDICAL PRODUCT?: ☐ YES ☐ NO	
WAS THE SUBJECT WITHDRAWN FROM THE STUDY DUE TO THE SAE? ☐ YES ☐ NO	

SERIOUS CRITERIA
☐ PATIENT DIED (EXITUS)
☐ LIFE THREATENING
☐ HOSPITALIZATION
☐ PROLONGED HOSPITALIZATION
☐ PERSISTENCE OR SIGNIFICANT DISABILITY/INCAPACITY
☐ CLINICALLY RELEVANT EVENT
☐ PREGNANCY

SEVERITY
☐ MILD
☐ MODERATE
☐ SEVERE
☐ LIFE THREATENING

¿HAS THE SERIOUS ADVERSE EVENT ENDED?
☐ YES ☐ NO

END DATE:
(DD/MM/YYYY)
_____

SAE OUTCOME:
☐ PERSISTENCE OF SAE
☐ RESOLVED WITHOUT SEQUELAE
☐ RESOLVED WITH SEQUELAE
☐ UNKNOWN
☐ EXITUS

II. SUSPECT DRUG INFORMATION

SUSPECT DRUG:	DAILY DOSE (Include units)	ROUTE	INDICATION FOR USE:	START DATE (dd/mm/yyyy):

ACTION TAKEN WITH SUSPECT DRUG:
☐ None ☐ Temporary interruption ☐ Permanent interruption ☐ Dose increase ☐ Dose decrease

INTERRUPTION DATE (dd/mm/yyyy):	REINTRODUCTION DATE (dd/mm/yyyy):

DID THE REACTION DIMINISH WHEN THE MEDICATION WAS SUSPENDED?	DID THE REACTION DIMINISH WHEN THE MEDICATION DOSE WAS DECREASED?	DID THE REACTION RE-APPEAR WHEN THE MEDICATION WAS RE-INTRUDUCED?
☐ YES ☐ NO ☐ NOT APPLY	☐ YES ☐ NO ☐ NOT APPLY	☐ YES ☐ NO ☐ NOT APPLY

Page 1 de 2

Serious Adverse Events Form
Vs 3.0 de 01sep2020 - English Vs.

III. CONCOMITNANT MEDICATIONS AND MEDICAL HISTORY

CONCOMITANT MEDICATION (Mark with an asterisk the suspect drug (s))	DAILY DOSE (Include units)	ROUTE	START DATE (dd/mm/yyyy)	END DATE (dd/mm/yyyy)	SAE TREATMENT (mark only if medication has been used to treat the SAE)	INDICATION (complete when medication has not been used to treat the SAE)
					☐	
					☐	
					☐	
					☐	
	RELEVANT INFORMATION OF THE MEDICAL HISTORY (ej. Diagnostics, allergies, pregnancies, etc.)					

IV. RELATIONSHIP OF THE CAUSALITY OF THIS SERIOUS ADVERSE EVENT TO THE SUSPECTED DRUG/S

INVESTIGATOR'S JUDGMENT:	SPONSOR'S JUDGMENT:
☐ Related ☐ Not related	☐ Related ☐ Not related

V. INFORMATION OF THE SPONSOR AND INVESTIGATOR

SPONSOR ADDRESS Fundación SEIMC-GESIDA C/ Agustín de Betancourt nº 13 - entreplanta 28003 Madrid	**NAME AND PHONE OF THE INVESTIGATOR WHO REPORT THE SAE:**
REPORT DATE (dd/mm/yyyy):	**COMPLEMENTARY REPORT ATTACHED** ☐ YES ☐ NO

INVESTIGATOR WHO COMPLETE THE REPORT:

Name: _____

Signature: _____

Date: _____

PERSONAL OF THE SPONSOR WHO RECEIVE THE REPORT:

Name: _____

Signature: _____

Reception date at SEIMC-GESIDA Foundation (DD/MM/YYYY):

APPENDIX 5: PREGNANCY NOTIFICATION FORM

CONFIDENTIAL

Protocol Identifier	Subject Identifier	Centre Number

PREGNANCY NOTIFICATION FORM

This form should be completed according to the protocol reporting requirements.
Note: Most protocols do not require collection of subject's partner pregnancy.
Complete this form for each subject or subject's partner who becomes pregnant during the study period. Send a copy of the form to FSG (Email or fax number +34 915542283).

Who is this form being completed for, ✓*one:* ☐ Subject

☐ Subject's partner

MOTHER'S RELEVANT MEDICAL/FAMILY HISTORY

Mother's year of birth ☐☐☐☐ Year

Date of last menstrual period ☐☐ Day ☐☐☐ Month ☐☐ Year

Estimated date of delivery ☐☐ Day ☐☐☐ Month ☐☐ Year

Was the mother using a method of contraception? ☐ Yes ☐ No

If Yes, specify: _____

Type of conception, ✓*one:* ☐ Normal (includes use of fertility drugs)
☐ IVF (in vitro fertilisation)

Relevant laboratory tests and procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling, including dates of tests and procedures).

_____

_____

Number of previous pregnancies ☐☐ Pre-term ☐☐ Full-term

If applicable, record the number in the appropriate categories below:

☐☐ Normal births
☐☐ Stillbirths
☐☐ Children born with defects
☐☐ Spontaneous abortion
☐☐ Elective abortion
☐☐ Other

Record details of children born with defects: _____

Are there any additional factors that may have an impact on the outcome of this pregnancy? ☐ Yes ☐ No

If Yes, specify: _____

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Subject Identifier	Centre Number
☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐	☐☐☐☐☐☐

PREGNANCY NOTIFICATION FORM (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

Only recorded if required by the protocol and Informed Consent of the father has been obtained.

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_____

_____

DRUG EXPOSURES

In the following table, list all medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). Enter the investigational product details on the first line (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.

Drug Name *(Trade Name preferred)*	Route of Admin. or For-mulation	Total Daily Dose	Units	Started Pre-Study Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Med-ication Y=Yes N=No	Reason for Medication

Was the subject withdrawn from the study as a result of this pregnancy? ☐ Yes ☐ No

REPORTING INVESTIGATOR INFORMATION (Forward to a more appropriate physician if needed)

Name _____ Title __ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ Day ☐☐☐ Month ☐☐ Year
(confirming that the data on these pages are accurate and complete)

Investigator's name (print) _____

Vs 1.0, date 25SEP2020.

APPENDIX 6: PREGNANCY FOLLOW-UP FORM

Protocol Identifier	Subject Identifier	Centre Number

PREGNANCY FOLLOW-UP FORM - CURRENT PREGNANCY INFORMATION

One form should be completed per foetus (e.g., if a subject is carrying twins a form should be completed for each twin).

Who is this form being completed for, ✓*one:* ☐ Subject ☐ Subject's partner

PREGNANCY STATUS

While pregnancy itself is not an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. A spontaneous abortion is always considered to be an SAE and will be reported as described in the protocol. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the Investigator will be reported to FSG per the protocol. Whilst the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Early termination, ✓*if applicable:*

☐ Stillbirth
☐ Foetal death
☐ Method used for delivery, *specify* _____
☐ Spontaneous abortion
☐ Elective abortion
☐ Other, *specify* _____

InForm studies:

- *If a female subject is pregnant and the outcomes/associated events fulfill the criteria of an SAE, complete the information in the eCRF SAE form and on this paper Pregnancy Follow-up form.*
- *If male subject's partner is pregnant and the outcomes/associated events fulfill the criteria of an SAE, then complete the information in the paper SAE form and send together with this paper Pregnancy Follow-up form.*

Paper studies: *If any of the outcomes/associated events fulfil the criteria of an SAE, complete the SAE section in the CRF.*

FOETAL/NEONATAL STATUS

☐ Normal
☐ Birth defect (i.e., structural/chromosomal disorder) *Complete Serious Adverse Event pages*
☐ Other disorder (e.g., non-structural, premature birth, intrauterine death/stillbirth)

If birth defects are diagnosed, is the origin of the defect known? ☐ Yes ☐ No

If Yes, specify _____

INFANT INFORMATION

Date of birth/miscarriage/termination ☐☐ Day ☐☐☐ Month ☐☐ Year

Gestational weeks at birth/miscarriage/termination ☐☐ Weeks

Infant's sex ☐ Male ☐ Female ☐ Unknown

Length ☐☐.☐ cm Weight ☐☐☐☐.☐☐ g

Apgar score (0 - 10) ☐☐ First assessment ☐☐ Second assessment

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Subject Identifier	Centre Number

PREGNANCY FOLLOW-UP FORM - CURRENT INFORMATION (Continued)

ADDITIONAL DETAILS (Provide additional details on current labour/delivery/discharge notes etc.)

_____

_____

_____

_____

DRUG EXPOSURES DURING PREGNANCY

Complete drug section for all drugs (including OTC/vaccines) taken by the mother during pregnancy. Do not include drugs that have already been included on the Pregnancy Notification Form.

Drug Name *(Trade Name preferred)*	Route of Admin. or For-mulation	Total Daily Dose	Units	Started Pre-Study Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Med-ication Y=Yes N=No	Reason for Medication

REPORTING INVESTIGATOR INFORMATION (Forward to a more appropriate physician if needed)

Name _____ Title ___ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ ☐☐☐ ☐☐
(confirming that the data on these pages are accurate and complete) Day Month Year

Investigator's name (print) _____

Vs 1.0, date 25SEP2020.

APPENDIX 7: LIVER EVENTS FORM

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER EVENT RECORD
FOR INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES

US:ENG (United States/English)

COMPLETION GUIDELINES FOR CASE REPORT FORMS (CRFS)

GENERAL INSTRUCTIONS FOR CRF COMPLETION

- Complete CRFs in English; answer all questions on every page unless directed otherwise.
- Print neatly and legibly; use a black ballpoint pen and press firmly so that all copies are legible.
- Do not write information on page margins.
- Avoid use of abbreviations and acronyms whenever possible. If abbreviations must be used, use only clear abbreviations that are in standard medical use, or those supplied on instructional pages in this CRF.
- Enter Protocol and Subject Identifier in the space provided at the top of each CRF page.
- Do not write the Subject's name or initials anywhere inside the CRF.
- Record all values in the units indicated on the CRF.
- Where boxes are provided in the CRF to record numbers, complete as follows, using leading zeroes if necessary: 6 recorded as 0 6.
- Ensure that information classified as "Other, specify" does not fit into one of the listed categories. Record a concise reason in the "specify" field that accompanies "Other", if "Other" is ✓.
- If extra pages need to be inserted between numbered CRF pages, do the following: insert the first extra page after the last numbered page in the section of the CRF affected (e.g., Concomitant Medications) and number the extra page as nn.01. Subsequent extra pages are then numbered nn.02, nn.03 etc.

MISSING INFORMATION

- Use the following abbreviations for missing information.
  - NA not available/not applicable
  - ND not done
  - UNK unknown
  - NR no result (to be used only for missing data recorded on Local Lab pages)

CRF CORRECTION PROCESS

- Draw a single line through an incorrect entry and write the correct information nearby.
- Initial and date all corrections, additions or deletions.
- DO NOT erase, write over, use correction fluid or tape, or re-copy the original page to correct errors.

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	

ACTION IS REQUIRED

LIVER EVENT RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INSTRUCTIONS

1. **Liver Event Record Completion**

   Complete this Liver Event Record for all possible, suspected, implied, and/or probable cases of liver event.

   For serious adverse events (SAE), please ensure data provided here is consistent with the SAE CRF. If the SAE CRF is updated, please resubmit to FSG.

2. **Inform Fundación SEIMC-GESIDA**

   Mail or fax (fax preferred) the completed Liver Event Record within one week of the clinical assessment for liver event to GlaxoSmithKline.

   Retain a copy of the Liver Event Record for your files.

Attention: Fundación SEIMC-GESIDA
C/Agustín de Betancourt, 13 Entreplanta
28003 Madrid

FAX: +34 91 554 22 83

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Subject Identifier

LIVER EVENT RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INFORMATION

Print clearly.

Investigator's Name _____

Site Number _____

Investigator's Address _____ (Institution)

_____ (Internal Address)

_____ (Street Address)

_____ (City, State, Province, Postal Code)

_____ (Country)

Investigator's Telephone Number _____

Investigator's E-Mail Address _____

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier	Visit Date (Day Month Year)

LIVER EVENTS

Visit Date - please enter the date of the lab sample collection which resulted in the subject meeting protocol defined liver event criteria. (This is likely to be a scheduled sample collection, so this 'Visit Date' may be the same as the visit date of that collection.)

Which liver chemistry result reached or exceeded protocol-defined investigational product stopping/interruption criteria? ✓ *all that apply*

[1] ☐ ALT (alanine aminotransferase)

[3] ☐ Total bilirubin

[7] ☐ Direct bilirubin

[8] ☐ INR

[OT] ☐ Other

When did the liver event occur?

[D] ☐ During the treatment period

[A] ☐ After the treatment period

If the liver event occurred during treatment period record start and stop date of investigational product for that treatment period.

If the liver event occurred after treatment period record start and stop date of investigational product for the most recent period prior to the liver event.

Start date of Investigational Product ☐☐ ☐☐☐ ☐☐ (Day Month Year)

End date of Investigational Product ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Subject Identifier

LIVER EVENTS (Continued)

Record the details of any Adverse Events or exacerbations of Adverse Events on the Non-Serious Adverse Event Form OR the Serious Adverse Event Form. Exacerbations of Adverse Events include increases in frequency and severity.

It is particularly important to record any significant hypotension immediately prior to or concomitant with ALT elevation.
It is particularly important to record any gallbladder or biliary disease, or pancreatitis, that occurred during the study.

Is the subject age 55 or older?

[Y] ☐ Yes [N] ☐ No

If female, is the subject pregnant?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not applicable

If Yes, ensure Pregnancy Notification Form has been completed.

Were any diagnostic imaging tests of the liver or hepatobiliary system performed (such as a liver ultrasound, computerized tomography or CAT scan, magnetic resonance imaging or MRI, or endoscopic retrograde cholangiopancreatography, or other)?

[Y] ☐ Yes [N] ☐ No

If Yes, were the results normal?

[Y] ☐ Yes [N] ☐ No

If No, record the details on the Imaging form. Ensure the overall diagnosis indicated by imaging is captured on the Non-Serious Adverse Event form or Serious Adverse Event form.

Were any liver biopsies performed?

[Y] ☐ Yes [N] ☐ No

If Yes, complete Liver Biopsy form.

Does the subject use herbals, complementary or alternative medicines, food supplements (vitamins) or illicit drugs?

[Y] ☐ Yes [N] ☐ No

If Yes, record on the appropriate Concomitant Medication form.

Did the subject fast or undergo significant dietary change in the past week?

[Y] ☐ Yes [N] ☐ No

Vs 1.0, date 25SEP2020.

LIVER EVENTS
DEFINITIONS

CURRENT MEDICAL CONDITIONS

Conditions from which the subject is currently suffering, regardless of how long they have been present. If the subject has had a recurring condition that is not present at the time of the assessment, it can be classed as current if, in the Investigator's opinion it is likely to recur during the study.

PAST MEDICAL CONDITIONS

Conditions from which the subject has suffered in the past, but are no longer present. A past condition may have stopped as recently as the day prior to being assessed.

NO MEDICAL CONDITION

No current or past condition.

Vs 1.0, date 25SEP2020.

ALCOHOL INTAKE AT ONSET OF LIVER EVENT
INVESTIGATOR INSTRUCTIONS

ALCOHOL CONVERTER

1 unit of alcohol in US = 1.5oz hard liquor, 1 beer, 4oz wine

1 unit of alcohol in UK = 1 measure of spirits, 1/2 pint beer, 1 small glass of wine (125ml)

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Subject Identifier

LIVER EVENTS (Continued)

MEDICAL CONDITIONS AT ONSET OF LIVER EVENT

Specific Condition ✓ *only one response for each condition*	Current [1]	Past [2]	No Medical Condition [5]
1. Acute Viral Hepatitis A			
2. Chronic Hepatitis B			
3. Chronic Hepatitis C			
4. Cytomegalovirus Hepatitis			
5. Epstein Barr Virus Infectious Mononucleosis			
6. Herpes Simplex Hepatitis			
7. Alcoholic Liver Disease			
8. Non-alcoholic Steatohepatitis			
9. Fatty Liver			
10. Hepatic Cirrhosis			
11. Hemochromatosis			
12. Autoimmune Hepatitis			
13. Gallbladder disease			
DRUG RELATED LIVER DISEASE CONDITIONS (All drugs including Investigational Product)			
14. Drug related liver disease			

OTHER LIVER DISEASE CONDITIONS

Specific Condition *Record only one per line for each condition and ✓ only one response for*	Current [1]	Past [2]
15.		
16.		

OTHER MEDICAL CONDITIONS

Specific Condition ✓ *only one response for each condition*	Current [1]	Past [2]	No Medical Condition [5]
17. Drug Allergies			
18. Rheumatoid Arthritis			
19. Psoriasis			
20. Thyroid Disease			
21. Inflammatory Bowel Disease			
22. Lupus			
23. Sjogren's Syndrome			
24. Vitiligo			

Vs 1.0, date 25SEP2020.

ALCOHOL INTAKE AT ONSET OF LIVER EVENT

Record the average number of units of alcohol[1] consumed per week ☐☐☐ units per week

If the subject does not drink enter '0'.

[1] *See facing page for conversion guidelines.*

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER EVENT RECORD (INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES) (Continued)

NARRATIVE/COMMENTS

Provide a textual description of the liver event including relevant medical history, the course of the reaction, any/all interruptions of liver therapy including dates, treatment required to stabilize the reaction, resolution/outcome, other contributing factors, alternative etiologies, and any other relevant information. Use additional pages as needed. *For serious AE (SAE), please use the SAE CRF for narrative description. If the SAE CRF is updated, please resubmit to GSK.*

US:ENG (United States/English)

LIVER EVENT RECORD (INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES) (Continued)

INVESTIGATOR'S SIGNATURE

The Investigator is accountable for this data. However, the Principal Investigator may delegate signature authority to a medically qualified Sub-investigator.

I confirm that I have reviewed the data in this report for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Investigator's Name (print) _____

US:ENG (United States/English)

APPENDIX 8: LIVER EVENTS BIOPSY FORM

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER EVENT BIOPSY RECORD
FOR INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES

US:ENG (United States/English)

COMPLETION GUIDELINES FOR CASE REPORT FORMS (CRFS)

GENERAL INSTRUCTIONS FOR CRF COMPLETION

- Complete CRFs in English; answer all questions on every page unless directed otherwise.
- Print neatly and legibly; use a black ballpoint pen and press firmly so that all copies are legible.
- Do not write information on page margins.
- Avoid use of abbreviations and acronyms whenever possible. If abbreviations must be used, use only clear abbreviations that are in standard medical use, or those supplied on instructional pages in this CRF.
- Enter Protocol and Subject Identifier in the space provided at the top of each CRF page.
- Do not write the Subject's name or initials anywhere inside the CRF.
- Record all values in the units indicated on the CRF.
- Where boxes are provided in the CRF to record numbers, complete as follows, using leading zeroes if necessary: 6 recorded as 0 6.
- Ensure that information classified as "Other, specify" does not fit into one of the listed categories. Record a concise reason in the "specify" field that accompanies "Other", if "Other" is ✓.
- If extra pages need to be inserted between numbered CRF pages, do the following: insert the first extra page after the last numbered page in the section of the CRF affected (e.g., Concomitant Medications) and number the extra page as nn.01. Subsequent extra pages are then numbered nn.02, nn.03 etc.

MISSING INFORMATION

- Use the following abbreviations for missing information.
  - NA not available/not applicable
  - ND not done
  - UNK unknown
  - NR no result (to be used only for missing data recorded on Local Lab pages)

CRF CORRECTION PROCESS

- Draw a single line through an incorrect entry and write the correct information nearby.
- Initial and date all corrections, additions or deletions.
- DO NOT erase, write over, use correction fluid or tape, or re-copy the original page to correct errors.

US:ENG (United States/English)

Protocol Identifier	

ACTION IS REQUIRED

LIVER EVENT BIOPSY RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INSTRUCTIONS

1. **Liver Event Biopsy Record Completion**

   Complete this Liver Event Biopsy Record for all possible, suspected, implied, and/or probable cases of liver event biopsy.

   For serious adverse events (SAE), please ensure data provided here is consistent with the SAE CRF. If the SAE CRF is updated, please resubmit to FSG.

2. **Inform GlaxoSmithKline**

   Mail or fax (fax preferred) the completed Liver Event Biopsy Record within one week of the clinical assessment for liver event biopsy to GlaxoSmithKline.

   Retain a copy of the Liver Event Biopsy Record for your files.

Attention:Fundación SEIMC-GESIDA

C/ Agustín de Betancourt, 13-Entreplanta
28003 - Madrid

FAX: +34 91 554 22 83

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER EVENT BIOPSY RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INFORMATION

Print clearly.

Investigator's Name _____

Site Number _____

Investigator's Address _____ (Institution)

_____ (Internal Address)

_____ (Street Address)

_____ (City, State, Province, Postal Code)

_____ (Country)

Investigator's Telephone Number _____

Investigator's E-Mail Address _____

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER BIOPSY

Complete a separate form for each liver biopsy performed.

Date of liver biopsy ☐☐ Day ☐☐☐ Month ☐☐ Year

Approximate size of liver biopsy ☐☐ mm *(number from 0 - 50)*

A. Final Diagnosis ✓*all that apply:*

- [A0] ☐ Normal
- [A1] ☐ Acute hepatitis
- [A2] ☐ Chronic hepatitis
- [A3] ☐ Cholestatic hepatitis
- [A4] ☐ Drug-induced cholestasis
- [A5] ☐ Acute viral hepatitis
- [A6] ☐ Chronic viral hepatitis
- [A7] ☐ Drug-induced hepatitis
- [A8] ☐ Autoimmune hepatitis
- [A9] ☐ Bridging necrosis
- [A10] ☐ Submassive hepatic necrosis
- [A11] ☐ Massive hepatic necrosis
- [A12] ☐ Steatosis - microvesicular
- [A13] ☐ Steatosis - macrovesicular
- [A14] ☐ Steatosis - mixed
- [A15] ☐ Non-alcoholic steatohepatitis
- [A16] ☐ Alcoholic hepatitis
- [A17] ☐ Hepatic granulomas
- [A18] ☐ Sarcoidosis
- [A19] ☐ Fibrosis
- [A20] ☐ Cirrhosis
- [A21] ☐ Primary biliary cirrhosis
- [A22] ☐ Primary sclerosing cholangitis
- [A23] ☐ Autoimmune overlap syndrome
- [A24] ☐ Hemochromatosis
- [A25] ☐ Alpha-1-antitrypsin deficiency
- [A26] ☐ Wilson's disease
- [A27] ☐ Veno-occlusive disease
- [A28] ☐ Budd-Chiari syndrome
- [A29] ☐ Neoplasia
- [A99] ☐ Other, *specify*: _____

B. Liver Architecture ✓*all that apply:*

- [B1] ☐ Normal
- [B2] ☐ Bridging fibrosis
- [B3] ☐ Diffuse fibrosis
- [B4] ☐ Nodular regenerative hyperplasia
- [B5] ☐ Congenital hepatic fibrosis
- [B6] ☐ Cirrhosis
- [B7] ☐ Centrilobular congestion
- [B8] ☐ Endophlebitis
- [B9] ☐ Veno-occlusive disease
- [B10] ☐ Canalicular cholestasis
- [B11] ☐ Apoptosis
- [B12] ☐ Focal (or spotty or mild) hepatocellular necrosis
- [B13] ☐ Interface hepatitis (periportal hepatitis or piecemeal necrosis)
- [B14] ☐ Ischaemic necrosis
- [B15] ☐ Centrolobular (Zone 3) necrosis
- [B16] ☐ Focal coagulative necrosis
- [B17] ☐ Centrolobular (Zone 3) coagulative necrosis
- [B18] ☐ Bridging hepatocellular necrosis
- [B19] ☐ Massive or panlobular hepatocellular necrosis
- [B20] ☐ Dysplasia
- [B21] ☐ Neoplasia
- [B99] ☐ Other, *specify*: _____

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER BIOPSY (Continued)

C. Description of Liver Cells or Hepatocytes ✓*all that apply:*

- [C0] ☐ Normal
- [C1] ☐ Ballooning
- [C2] ☐ Acidophilic
- [C3] ☐ Pseudoxanthomatous
- [C4] ☐ Multinucleated giant hepatocytes
- [C99] ☐ Other, *specify:* _____

D. Liver Cell or Hepatocyte Inclusions or Vacuoles ✓*all that apply:*

- [D0] ☐ No inclusions
- [D1] ☐ Macrovesicular steatosis
- [D2] ☐ Microvesicular steatosis
- [D3] ☐ Bile accumulation
- [D4] ☐ Diastase-resistant, PAS-positive cytoplasmic inclusions
- [D5] ☐ Alpha-1-antitrypsin inclusions
- [D6] ☐ Megamitochondria
- [D7] ☐ Mallory bodies
- [D8] ☐ "Ground Glass" inclusions
- [D9] ☐ Lipofuscin pigment
- [D10] ☐ Hemosiderin granules
- [D11] ☐ Orcein-positive cytoplasmin granules
- [D12] ☐ Protoporphyrin crystals (birefringent under polarised light)
- [D13] ☐ Uroporphyrin crystals (red fluorescence under ultraviolet light)
- [D99] ☐ Other, *specify:* _____

E. Hepatocyte or Liver Cell Nuclear Abnormalities ✓*all that apply:*

- [E0] ☐ None
- [E1] ☐ Hepatocellular mitoses
- [E2] ☐ Binucleated or multinucleated hepatocytes
- [E3] ☐ CMV inclusion bodies
- [E4] ☐ HSV inclusions
- [E5] ☐ Varicella inclusions
- [E99] ☐ Other, *specify:* _____

F. Liver or Lobular Infiltrates ✓*all that apply:*

- [F0] ☐ None
- [F1] ☐ Eosinophils
- [F2] ☐ Lymphocytes
- [F3] ☐ Plasma cells
- [F4] ☐ Neutrophils
- [F5] ☐ Macrophages and proliferating Kupffer cells
- [F6] ☐ Granulomas
- [F99] ☐ Other, *specify:* _____

G. Portal Tract Inflammation ✓*all that apply:*

- [G0] ☐ None
- [G1] ☐ Eosinophils
- [G2] ☐ Lymphoid aggregates and/or follicles
- [G3] ☐ Plasma cells
- [G4] ☐ Neutrophils
- [G5] ☐ Histocytes and macrophages
- [G99] ☐ Other, *specify:* _____

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier
☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐	☐☐☐☐☐☐

LIVER BIOPSY (Continued)

H. Bile Ducts ✓*all that apply:*

- [H0] ☐ Normal
- [H1] ☐ Proliferation of bile ducts (bile ductular reaction)
- [H2] ☐ Dilation, degeneration or disruption of portal bile ducts
- [H3] ☐ Paucity of bile ducts
- [H4] ☐ Periductal fibrosis
- [H99] ☐ Other, *specify:* _____

I. Portal Veins ✓*all that apply:*

- [I0] ☐ Normal
- [I1] ☐ Pyelophlebitis
- [I2] ☐ Thrombosis, sclerosis or occlusion of portal vein
- [I3] ☐ Neoplastic invasion of portal vein
- [I4] ☐ Granulomatous compression of portal vein
- [I99] ☐ Other, *specify:* _____

J. Liver Infections ✓*all that apply:*

- [J0] ☐ Normal
- [J1] ☐ Leishmaniasis donovani
- [J2] ☐ Plasmodium falciparum
- [J3] ☐ Toxoplasmosis
- [J4] ☐ Cryptococcus neoformans
- [J5] ☐ Histoplasma capsulatum
- [J6] ☐ Mycobacterium tuberculosis
- [J7] ☐ Other mycobacterial species
- [J99] ☐ Other, *specify:* _____

K. Parasites or Ova ✓*all that apply:*

- [K0] ☐ None
- [K1] ☐ Schistosome and/or ova
- [K2] ☐ Ascaris and/or ova
- [K3] ☐ Toxocara and/or ova
- [K4] ☐ Echinococcus cysts
- [K5] ☐ Hepatic capillariasis worms and/or ova
- [K99] ☐ Other, *specify:* _____

L. Histologic Staining or Additional Studies Obtained ✓*all that apply:*

- [L1] ☐ Haematoxylin and eosin (or H & E)
- [L2] ☐ Masson
- [L3] ☐ Toluidine blue or Giemsa
- [L4] ☐ Prussian blue
- [L5] ☐ Periodic Acidic Schiff (PAS), with or without diastase
- [L6] ☐ Oil red O
- [L7] ☐ Congo red
- [L8] ☐ Hall's stain
- [L9] ☐ Gridley's stain
- [L10] ☐ Rhodanine (copper)
- [L11] ☐ Rubeanic acid (copper)
- [L12] ☐ Orcein, aldehyde fuchsin or Victoria blue
- [L13] ☐ Electron microscopy
- [L14] ☐ Hepatitis A immunostains positive
- [L15] ☐ Hepatitis B core antigen or hepatitis B surface antibody immunostains positive
- [L16] ☐ Hepatitis D immunostains
- [L17] ☐ Other immunostains
- [L99] ☐ Other, *specify:* _____

Vs 1.0, date 25SEP2020.

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER EVENT BIOPSY RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES) (Continued)
NARRATIVE/COMMENTS

Provide a textual description of the liver event biopsy including relevant medical history, the course of the reaction, any/all interruptions of liver therapy including dates, treatment required to stabilize the reaction, resolution/ outcome, other contributing factors, alternative etiologies, and any other relevant information. Use additional pages as needed. *For serious AE (SAE), please use the SAE CRF for narrative description. If the SAE CRF is updated, please resubmit to FSG.*

US:ENG (United States/English)

LIVER EVENT BIOPSY RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES) (Continued)
INVESTIGATOR'S SIGNATURE

The Investigator is accountable for this data. However, the Principal Investigator may delegate signature authority to a medically qualified Sub-investigator.

I confirm that I have reviewed the data in this report for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Investigator's Name (print) _____

US:ENG (United States/English)

Ve 1.0, date 25SEP2020.

APPENDIX 9: POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT FORM

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT
FOR INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES

US:ENG (United States/English)

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT

INSTRUCTIONS FOR COMPLETING POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT FORMS

Complete the "Possible Suicidality-Related Adverse Event" CRF Form if there is an occurrence of an adverse event which, in the investigator's judgement, is a possible suicidality-related event. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide.

The event must also be reported on the Serious Adverse Events (SAE) CRF using the same terminology. **Please ensure data provided here is consistent with the SAE CRF.**

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	

COMPLETION GUIDELINES FOR CASE REPORT FORMS (CRFS)

GENERAL INSTRUCTIONS FOR CRF COMPLETION

- Complete CRFs in English; answer all questions on every page unless directed otherwise.
- Print neatly and legibly; use a black ballpoint pen and press firmly so that all copies are legible.
- Do not write information on page margins.
- Avoid use of abbreviations and acronyms whenever possible. If abbreviations must be used, use only clear abbreviations that are in standard medical use, or those supplied on instructional pages in this CRF.
- Enter Protocol and Subject Identifier in the space provided at the top of each CRF page.
- Do not write the Subject's name or initials anywhere inside the CRF.
- Record all values in the units indicated on the CRF.
- Where boxes are provided in the CRF to record numbers, complete as follows, using leading zeroes if necessary: 6 recorded as [0][6].
- Ensure that information classified as "Other, specify" does not fit into one of the listed categories. Record a concise reason in the "specify" field that accompanies "Other", if "Other" is ✓.
- If extra pages need to be inserted between numbered CRF pages, do the following: insert the first extra page after the last numbered page in the section of the CRF affected (e.g., Concomitant Medications) and number the extra page as nn.01. Subsequent extra pages are then numbered nn.02, nn.03 etc.

MISSING INFORMATION

- Use the following abbreviations for missing information.
  - NA not available/not applicable
  - ND not done
  - UNK unknown
  - NR no result (to be used only for missing data recorded on Local Lab pages)

CRF CORRECTION PROCESS

- Draw a single line through an incorrect entry and write the correct information nearby.
- Initial and date all corrections, additions or deletions.
- DO NOT erase, write over, use correction fluid or tape, or re-copy the original page to correct errors.

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	

ACTION IS REQUIRED

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT RECORD (INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INSTRUCTIONS

Mail or fax (fax preferred) the completed Possible Suicidality-Related Adverse Event Record within one week of the clinical assessment for Possible Suicidality-Related Adverse Event to Fundación SEIMC-GESIDA.

Retain a copy of the Possible Suicidality-Related Adverse Event Record for your files.

Attention: Fundación SEIMC-GESIDA
C/ Agustín de Betancourt nº 13 - entreplanta
Madrid 28003

Fax: +34 915542283

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT RECORD (INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INFORMATION

Print clearly.

Investigator's Name _____

Site Number _____

Investigator's Address _____ (Institution)

_____ (Internal Address)

_____ (Street Address)

_____ (City, State, Province, Postal Code)

_____ (Country)

Investigator's Telephone Number _____

Investigator's E-Mail Address _____

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Subject Identifier

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT

SECTION 1

If the subject experienced a possible suicidality-related adverse event as assessed by the investigator during the study, provide information below.

Note: Review SAE CRF pages already provided and if further information is available, update and resubmit the SAE CRF.

Event	Start Date Day Month Year
e.g., Fleeting suicidal thoughts	*25 Jan 14*

SECTION 2 Possible Cause(s) of Possible Suicidality-related Adverse Event:

Disease under study	[Y] ☐ Yes	[N] ☐ No	Withdrawal of study treatment(s)	[Y] ☐ Yes	[N] ☐ No
Concomitant medication(s) *Record in Section 8*	[Y] ☐ Yes	[N] ☐ No	Study treatment dose change	[Y] ☐ Yes	[N] ☐ No
Comorbid psychiatric condition(s) *Record in Section 8*	[Y] ☐ Yes	[N] ☐ No	Lack of efficacy	[Y] ☐ Yes	[N] ☐ No
Medical condition(s) *Record in Section 8*	[Y] ☐ Yes	[N] ☐ No	Study treatment(s)	[Y] ☐ Yes	[N] ☐ No
Psycho-social stressors *Record in Section 5*	[Y] ☐ Yes	[N] ☐ No	Other, *specify* _____		

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Subject Identifier

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT (Continued)

SECTION 3 Provide this information, including timeframe(s) where possible:

1. Has the subject had any psychiatric conditions in the past?	[Y] ☐ Yes [N] ☐ No	*If Yes, provide information:* _____ _____
2. Has the subject had any suicidal ideation, behaviour or self-harm in the past?	[Y] ☐ Yes [N] ☐ No	*If Yes, provide information:* _____ _____
3. Subject's current use of illicit drugs?	[Y] ☐ Yes [N] ☐ No	*If Yes, provide information, including results of a drug screen test if one has been obtained:* _____ _____
4. Subject's current use of alcohol?	[Y] ☐ Yes [N] ☐ No	*If Yes, provide information, including results of an alcohol level test if one has been obtained:* _____ _____
5. Family history of suicidality?	[Y] ☐ Yes [N] ☐ No [U] ☐ Unk	*If Yes, provide information:* _____ _____
6. Family history of psychiatric disorders?	[Y] ☐ Yes [N] ☐ No [U] ☐ Unk	*If Yes, provide information:* _____ _____

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Subject Identifier

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT (Continued)

SECTION 4 Provide information on the subject's current psycho-social stressors. For example, isolation, problems with family, relationships, work, finances, stress, etc.
SECTION 5 Provide information on any relevant and/or recent suicidal ideation, not associated with suicidal behaviour, as assessed by the investigator, for this index event i.e., provide details, including any suicidal thoughts, and associated frequency, severity and duration, as well as likelihood of the subject acting upon these thoughts.

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Subject Identifier

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT (Continued)

SECTION 6 Provide information on any suicidal behaviour present during the study, as assessed by the investigator, for this index event, i.e.
• Details of any suicidal behaviour, including any plan, preparations, and/or attempt • Description of the associated frequency, severity and duration of these behaviours • Likelihood of the subject acting upon plans and preparations • If possible, description of the subject's intent (or evidence of attention seeking behaviour) • Description of the degree of impulsivity or premeditation • Description of the subject's mood and thoughts before and after the behaviour
SECTION 7 Provide any additional comments or explanation, including, but not limited to, both medical and psychiatric treatment, outcome and follow-up.

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	

POSSIBLE SUICIDALITY-RELATED ADVERSE EVENT RECORD (INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES) (Continued)
INVESTIGATOR'S SIGNATURE
INVESTIGATOR INSTRUCTIONS

The Investigator is accountable for this data. However, the Principal Investigator may delegate signature authority to a medically qualified Sub-investigator.

US:ENG (United States/English)

INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this report for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's Signature: _____ Date ☐☐ ☐☐☐ ☐☐
Day Month Year

Investigator's Name (print) _____

US:ENG (United States/English)

APPENDIX 10: LIVER IMAGING RECORD

CONFIDENTIAL

Protocol Identifier	Site Identifier	Subject Identifier

LIVER IMAGING RECORD
FOR INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES

US:ENG (United States/English)

COMPLETION GUIDELINES FOR CASE REPORT FORMS (CRFS)

GENERAL INSTRUCTIONS FOR CRF COMPLETION

- Complete CRFs in English; answer all questions on every page unless directed otherwise.
- Print neatly and legibly; use a black ballpoint pen and press firmly so that all copies are legible.
- Do not write information on page margins.
- Avoid use of abbreviations and acronyms whenever possible. If abbreviations must be used, use only clear abbreviations that are in standard medical use, or those supplied on instructional pages in this CRF.
- Enter Protocol and Subject Identifier in the space provided at the top of each CRF page.
- Do not write the Subject's name or initials anywhere inside the CRF.
- Record all values in the units indicated on the CRF.
- Where boxes are provided in the CRF to record numbers, complete as follows, using leading zeroes if necessary: 6 recorded as 0 6.
- Ensure that information classified as "Other, specify" does not fit into one of the listed categories. Record a concise reason in the "specify" field that accompanies "Other", if "Other" is ✓.
- If extra pages need to be inserted between numbered CRF pages, do the following: insert the first extra page after the last numbered page in the section of the CRF affected (e.g., Concomitant Medications) and number the extra page as nn.01. Subsequent extra pages are then numbered nn.02, nn.03 etc.

MISSING INFORMATION

- Use the following abbreviations for missing information.
  - NA not available/not applicable
  - ND not done
  - UNK unknown
  - NR no result (to be used only for missing data recorded on Local Lab pages)

CRF CORRECTION PROCESS

- Draw a single line through an incorrect entry and write the correct information nearby.
- Initial and date all corrections, additions or deletions.
- DO NOT erase, write over, use correction fluid or tape, or re-copy the original page to correct errors.

US:ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	

ACTION IS REQUIRED

LIVER IMAGING RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INSTRUCTIONS

1. **Liver Imaging Record Completion**

   Complete this Liver Imaging Record for all possible, suspected, implied, and/or probable cases of liver imaging.

   For serious adverse events (SAE), please ensure data provided here is consistent with the SAE CRF. If the SAE CRF is updated, please resubmit to FSG.

2. **Inform Fundación SEIMC-GESIDA**

   Mail or fax (fax preferred) the completed Liver Imaging Record within one week of the clinical assessment for liver imaging to Fundación SEIMC-GESIDA.

   Retain a copy of the Liver Imaging Record for your files.

Attention: Fundación SEIMC-GESIDA

C/Agustín de Betancourt, 13 - Entreplanta
28003 Madrid

FAX: +34 91 554 22 83

US.ENG (United States/English)

CONFIDENTIAL

Protocol Identifier	Subject Identifier	

LIVER IMAGING RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES)
INVESTIGATOR INFORMATION

Print clearly.

Investigator's Name	_____	
Site Number	_____	
Investigator's Address	_____	(Institution)
	_____	(Internal Address)
	_____	(Street Address)
	_____	(City, State, Province, Postal Code)
	_____	(Country)
Investigator's Telephone Number	_____	
Investigator's E-Mail Address	_____	

US:ENG (United States/English)

CONFIDENTIAL

Protocol identifier	Site identifier	Subject identifier

LIVER IMAGING

Complete a separate form for each individual imaging test performed.

Date of hepatic or liver imaging test: Day ☐☐ Month ☐☐☐ Year ☐☐

What method was used for this imaging test? ✓ one: *(if more than one imaging test was performed, complete a separate form for each test).*

- [1] ☐ Ultrasound - transabdominal
- [2] ☐ Ultrasound - endoscopic
- [3] ☐ Magnetic Resonance Imaging (MRI)
- [4] ☐ Computerised Tomography (CT)
- [5] ☐ Endoscopic Retrograde Cholangiopancreatography (ERCP)
- [6] ☐ Positron Emission Tomography (PET)
- [7] ☐ Positron Emission Tomography/Computed Tomography (PET/CT)
- [UT] ☐ Other, specify: _____

Are images technically adequate? ✓ one:

- [1] ☐ Optimal
- [2] ☐ Readable, but not optimal
- [3] ☐ Not readable
- [UT] ☐ Other, specify: _____

A. Indicate the liver size ✓ one:

- [A 1] ☐ Normal size
- [A 2] ☐ Hypertrophy (or enlarged)
- [A 3] ☐ Atrophy (or smaller than normal)
- [A 4] ☐ Segmental hypertrophy
- [A 9 9] ☐ Other, specify: _____

B. Indicate the liver texture ✓ one:

- [B 1] ☐ Normal
- [B 2] ☐ Heterogeneous
- [B 3] ☐ Suggestive of fibrosis
- [B 4] ☐ Nodular or suggestive of cirrhosis
- [B 9 9] ☐ Other, specify: _____

C. Grade the diffuse and/or geographic fatty infiltrate of the liver ✓ one:

- [C 1] ☐ Not applicable - no fatty infiltration
- [C 2] ☐ Mild (≤25%)
- [C 3] ☐ Moderate (>25% to <75%)
- [C 4] ☐ Severe (≥75%)
- [C 9 9] ☐ Other, specify: _____

D. Ascites present ✓ one:

- [D 1] ☐ None present
- [D 2] ☐ Yes - small amount
- [D 3] ☐ Yes - moderate or severe amount
- [D 9 9] ☐ Other, specify: _____

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LIVER IMAGING (Continued)

E. Are Focal Hepatic Lesions characterisable? ✓*all that apply:*

- [E 0] ☐ Not applicable - no hepatic lesions
- [E 1] ☐ Solid
- [E 2] ☐ Cystic
- [E 3] ☐ Hemangioma
- [E 4] ☐ Focal Nodular Hyperplasia
- [E 99] ☐ Other, specify: _____

F. Gallstones or gallbladder lesions? ✓*all that apply:*

- [F 0] ☐ None
- [F 1] ☐ Gallstones
- [F 2] ☐ Gallbladder polyp(s)
- [F 3] ☐ Sludge
- [F 4] ☐ Gallbladder wall thickening/oedema
- [F 5] ☐ Gallbladder wall gas
- [F 6] ☐ Cholecystitis
- [F 7] ☐ Gallbladder wall calcification
- [F 8] ☐ Gallbladder mass
- [F 99] ☐ Other, specify: _____

G. Biliary ductal lesions? ✓*all that apply:*

- [G 0] ☐ None
- [G 1] ☐ Intrahepatic ductal dilation (focal involving the right hepatic lobe)
- [G 2] ☐ Intrahepatic dutal dilation (focal involving the left hepatic lobe)
- [G 3] ☐ Intrahepatic ductal dilation (involving both right and left hepatic lobes)
- [G 4] ☐ Extrahepatic ductal dilation
- [G 5] ☐ Diffuse ductal dilation (involving both intrahepatic and extrahepatic ducts)
- [G 6] ☐ Acute Cholangitis
- [G 7] ☐ Primary sclerosing cholangitis
- [G 8] ☐ Choledocholithiasis (gallstone in duct)
- [G 9] ☐ Ductal filling defect(s), other than gallstone
- [G 10] ☐ Ductal wall thickening or oedema
- [G 11] ☐ Choledochal cyst
- [G 12] ☐ Ductal mass
- [G 13] ☐ Extrinsic mass compressing bile duct(s)
- [G 99] ☐ Other, specify: _____

H. Portal/Hepatic vein abnormalities? ✓*all that apply:*

- [H 0] ☐ None
- [H 1] ☐ Portal vein enlargement
- [H 2] ☐ Hepatic vein enlargement
- [H 3] ☐ Nonocclusive portal vein thrombosis
- [H 4] ☐ Occlusive portal vein thrombosis - bland
- [H 5] ☐ Hepatic vein thrombosis - bland
- [H 6] ☐ Occlusive portal vein thrombosis - malignant
- [H 7] ☐ Hepatic vein thrombosis - malignant
- [H 8] ☐ Involvement of the main portal vein
- [H 9] ☐ Involvement of the right portal vein
- [H 10] ☐ Involvement of the left portal vein
- [H 11] ☐ Budd-Chiari syndrome
- [H 99] ☐ Other, specify: _____

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Protocol Identifier	Site Identifier	Subject Identifier

LIVER IMAGING RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES) (Continued)
NARRATIVE/COMMENTS

Provide a textual description of the liver imaging including relevant medical history, the course of the reaction, any/all interruptions of liver therapy including dates, treatment required to stabilize the reaction, resolution/outcome, other contributing factors, alternative etiologies, and any other relevant information. Use additional pages as needed. *For serious AE (SAE), please use the SAE CRF for narrative description. If the SAE CRF is updated, please resubmit to FSG.*

US:ENG (United States/English)

LIVER IMAGING RECORD
(INVESTIGATOR SPONSORED/ViiV SUPPORTED STUDIES) (Continued)
INVESTIGATOR'S SIGNATURE

The investigator is accountable for this data. However, the Principal Investigator may delegate signature authority to a medically qualified Sub-investigator.

I confirm that I have reviewed the data in this report for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's Signature: _____ Date: ☐☐ (Day) ☐☐☐ (Month) ☐☐ (Year)

Investigator's Name (print) _____

US:ENG (United States/English)