STATISTICAL ANALYSIS PLAN ADDENDUM FOR FINAL ANALYSIS

Study Title:	A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of Switching to Tenofovir Alafenamide (TAF) from Tenofovir Disoproxil Fumarate (TDF) and/or Other Oral Antiviral Treatment (OAV) in Virologically Suppressed Chronic Hepatitis B Subjects with Renal and/or Hepatic Impairment
Name of Test Drug:	Tenofovir Alafenamide (TAF)
Study Number:	GS-US-320-4035
Protocol Version (Date):	Amendment 1 (23 May 2017)
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	05 October 2020
Analysis Plan Author(s):	PPD
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF IN-TEXT TABLES

This statistical analysis plan (SAP) addendum describes the statistical analyses and data presentations to be added or modified for the Final Clinical Study Report (CSR) for the Phase 2 Study GS-US-320-4035. This SAP addendum is based on the approved SAP dated 09 May 2019. The SAP addendum will be finalized before data finalization. Any changes made after the finalization of the SAP addendum will be documented in the final CSR.

1. ASSESSMENT OF COVID-19 IMPACT

This study was ongoing during the novel coronavirus (2019 nCOV [COVID-19]) pandemic, which has caused a disruption in the regular visit schedules for this study. Some study subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section provides guidance on handling special situations due to the COVID-19 pandemic in the final analysis.

Adverse events (AEs) attributed as being due to the COVID-19 pandemic will be included in all AE analyses specified in the SAP, if applicable. A by-subject listing of all AEs due to the COVID-19 pandemic will be provided.

1.1. Study Drug or Study Discontinuation Due to the COVID-19 Pandemic

A by-subject listing of reasons for premature study drug or study discontinuation due to the COVID-19 pandemic will be provided.

1.2. Protocol Deviations Due to the COVID-19 Pandemic

By-subject listings will be provided for subjects with important and non-important protocol deviations due to the COVID-19 pandemic, respectively.

1.3. Missed or Virtual Visits Due to the COVID-19 Pandemic

Information regarding missed or virtual visits due to the COVID-19 pandemic will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to the COVID-19 pandemic will be done using a Natural Language Processing (NLP) algorithm by analyzing the CRF comment fields. A detailed explanation of the algorithm is provided in Appendix 1.

A by-subject listing of subjects with missed or virtual visits due to the COVID-19 pandemic will be provided by subject ID number in ascending order.

2. ANALYSIS WINDOWS FOR WEEK 96

For the final analysis, no upper limit will be applied to the Week 96 analysis window in Table 3-2 to Table 3-8 in the SAP.

3. IMPUTATION FOR LAST DOSE DATE

If the last dose date is completely missing, please refer to the SAP Section 3.8.1 for imputation rules.

If the last dose date is partially missing, the latest of non-missing study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates will be used to impute the last dose date if the imputed month/year is no earlier than the partial last dose month/year (if month/year is not missing).

4. SERUM CREATININE CORRECTION

A positive shift in serum creatinine values was observed due to a lot calibration change on 01 July, 2018, occurring across Covance laboratory sites worldwide. A correction was therefore applied to records on or after 01 July, 2018 to serum creatinine, following the regression equation specified in Table 4-1. The corrected serum creatinine values will be used for the analyses of serum creatinine, serum creatinine toxicity, eGFR estimated by the Cockcroft Gault formula, eGFR by the CKD-EPI method and other relevant parameters.

The corrected values must be in the same unit as the original values after going through the regression formula in Table 4-1.

- If the unit of serum creatinine is "µmol/L", then use the formula directly.
- If the unit of serum creatinine is "mg/dL", the values should be converted to "µmol/L" before using the formula.

After the correction, unit of serum creatinine should be converted back to "mg/dL" for summary and comparison purpose.

Table 4-1. Method of Serum Creatinine Correction

Regional Lab Center	Accession Number[a]	Regular Regression for Serum Creatinine (µmol/L)[b,c]
Indianapolis	starts with 65	Y=1.002×X+1.77
Geneva	starts with 62 or 63	Y=1.025×X+2.62
Shanghai	starts with 67	Y=0.971×X+5.42
Singapore	starts with 64 or 66	Y=1.009×X−1.42
Japan	start with 68	Y=1.033×X+7.25

a Accession numbers specified which regional lab center tested the sample. For example, samples with accession number starting with 65 were tested in Indianapolis Auto Chemistry Center.
b X and Y are the serum creatinine values from previous lot before 01 July, 2018 and serum creatinine values from new lot on or after 01 July, 2018, respectively.
c The serum creatinine correction is based on the unit of umol/L. The unit should be converted to mg/dL for summary purposes.

5. APPENDICES

Appendix 1. Determining Missed and Virtual visits due to the COVID-19 Pandemic

This appendix describes the site collection of COVID-19 data as pertains to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should have entered "Visit missed due to COVID-19." If a visit which was to be conducted in-person was conducted virtually, sites should have entered "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

Natural Language Processing (NLP) was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see Table 1) and "Virtual" (or synonyms, see Table 1). The search terms are maintained in a global lookup and can be modified and/or corrected to tune the NLP model. For each comment field the following algorithm was applied:

STEP 1: Eliminate extraneous text from each comment field, e.g. "and", "or", "for", etc. This is done using the list of extraneous terms given in Table 2.

STEP 2: Check each of the remaining comment text strings against the "COVID-19" terms and "Virtual" terms with the Levenshtein distance, using SAS function COMPGED (computes a generalized edit distance using the Levenshtein operations to compute/summarize the degree of difference between two text strings):

i. f Levenshtein distance < 149 for any of the "COVID-19" terms then COVIDFL 1, else COVIDFL 0
ii. If Levenshtein distance < 149 for any of the "Virtual" terms then VIRTFL 1, else VIRTFL 0

STEP 3: For any comments with COVIDFL 1, assign "Missed visit" or "Virtual visit" as follows

i. IF COVIDFL 1 and the visit date is missing then result is 'Missed Visit'
ii. IF COVIDFL 1 and VIRTFL 1 then result is 'Virtual Visit'
iii. Otherwise result is missing

Table 1. Examples of search terms for "COVID-19" and "Virtual" used to identify missed and virtual visits

Search terms for "COVID-19"	Search terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Table 2. Examples of extraneous text terms to eliminate from the comment fields

a	down	in	she'd	Until
about	during	into	she'll	Up
above	each	is	she's	Very
after	few	it	should	Was
again	for	its	so	We
against	from	it's	some	we'd
all	further	itself	such	we'll
am	had	i've	than	Were
an	has	let's	that	we're
and	have	me	that's	we've
any	having	more	the	What
are	he	most	their	what's
as	he'd	my	theirs	When
at	he'll	myself	them	when's
be	her	nor	themselves	Where
because	here	of	then	where's
been	here's	on	there	Which
before	hers	once	there's	While
being	herself	only	these	Who
below	he's	or	they	Whom
between	him	other	they'd	who's
both	himself	ought	they'll	Why
but	his	our	they're	why's
by	how	ours	they've	With
could	how's	ourselves	this	Would
did	i	out	those	You
do	i'd	over	through	you'd
does	if	own	to	you'll
doing	i'll	same	too	Your
down	i'm	she	under	you're
	you've	yourself	yourselves	Yours

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
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