SymITA:

Switch to DRV/COB/FTC/TAF from Integrase containing regimens to evaluate changes in Tolerability/Adherence

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AE	Adverse Event
ART	Anti-retroviral Therapy
BMI	Body Mass Index
CBC	Complete Blood Count
CD4	helper T lymphocytes positive for surface glycoprotein CD4
CI	confidence interval
CMP	Complete Metabolic Panel
COB	Cobicistat
DRV	Darunavir
FDC	fixed dose combination
FTC	Emtricitabine
HBsAg	hepatitis B virus surface antigen serology
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human Immunodeficiency Virus-1
HIV-SI	HIV Symptom Index
IRB	institutional review board
MAAS	Midland Antiviral Adherence Survey
PII	Personal Identifying Information
PRO	Patient Reported Outcome survey
STR	Single Tablet Regimen
TAF	tenofovir alafenamide
SEA	Serious Adverse Event
VL	viral load

1. Introduction

Human Immunodeficiency Virus-1 (HIV) is a life threatening and serious infection throughout the world. The World Health Organization estimates between 30-43 million people are living with HIV worldwide. The natural progression of the disease cripples the immune system, leading to unchecked infections and ultimately death.

With the advent of anti-retroviral therapy, HIV transformed from a terminal infection into a manageable chronic disease for patients who were able to obtain medications, provided they could remain adherent to them.

When single tablet regimens (STR) became available, adherence to HIV medications was made easier for many patients. However even years after STR became available, 38% of patients reported they do not maintain optimal adherence to their HIV medications[1]. While there are many factors that contribute to this problem, medication intolerance contributes to suboptimal adherence for many patients[2].

2. Rationale for the Study

Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COB/FTC/TAF) is a coformulated STR, is the only protease inhibitor based STR, and is noted for its high tolerability[3]. These traits have the potential to improve adherence in patients who have intolerance to the integrase inhibitor class. We propose a two part study design to evaluate if patients who have suboptimal adherence due to integrase inhibitor intolerance may better tolerate Symtuza and subsequently have improved adherence.

3. Study Objectives

3.1. Part 1

3.1.1. Primary Objectives

3.1.1.1. To assess degree of adherence to ART in a real world setting

3.1.2. Secondary Objectives

3.1.2.1. To evaluate trends and patterns in subjects who report suboptimal adherence

3.2. Part 2

3.2.1. Primary Objectives

3.2.1.1. To determine potential changes in ART adherence in subjects who report suboptimal adherence due to side effects from integrase containing regimens switching to Symtuza.

3.2.2. Secondary Objectives

3.2.2.1. To evaluate the tolerability of switching from integrase containing regimen to Symtuza with the aid of Patient Reported Outcomes (PRO) questionnaire and number of drug discontinuation for any reason

3.2.2.2. To determine the safety of switching from integrase containing regimen to Symtuza in subjects with HIV-1 infection as determined by the proportion of participants with virologic failure, a change in laboratory parameters, and change in CD4 cell count from baseline.

3.2.2.3. To evaluate for potential weight loss when switching from integrase containing regimen to Symtuza

4. Study Endpoints

4.1. Part 1

4.1.1. Primary Endpoint

4.1.1.1. Percentage of subjects reporting suboptimal adherence

4.1.2. Secondary Endpoint

4.1.2.1. Percentage of subjects who report suboptimal adherence due to tolerance issues/side effects

4.1.2.2. Percentage of subjects who report suboptimal adherence due to reasons other than tolerance issues/side effects

4.2. **Part 2**

4.2.1. Primary Endpoint:

4.2.1.1. Change in adherence from baseline to 4 months, measured by adherence surveys

4.2.2. Secondary Endpoints:

4.2.2.1. Change at 4 months from baseline in tolerability measured by standardized patient reported outcome questionnaire

4.2.2.2. Proportion of subjects that have HIV-1 RNA ≥ 50 copies/mL at baseline and at Week 16

4.2.2.3. Proportion of subjects with significant changes at 4 months from baseline in serum creatinine, AST or ALT

4.2.2.4. Change at 4 months from baseline in absolute and percentage CD4.

4.2.2.5. Change at 4 months from baseline in absolute and percentage weight

4.2.2.6. Number of drug discontinuation for any reason

4.2.2.7. Compare adherence measured by adherence surveys on week 4 and Week 16 to the pill counts from week 4 and Week 16.

5. Study Drug

5.1. Formulation

5.1.1. SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) is an FDA approved fixed-dose combination tablet complete regimen for the treatment of HIV-1 infection in adults: • who have no prior antiretroviral treatment history or • who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.. • Darunavir is an inhibitor of the HIV-1 protease. • Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. • Emtricitabine, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI). • Tenofovir alafenamide, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. SYMTUZA tablets are for oral administration. Each tablet contains darunavir ethanolate equivalent to 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 11.2 mg of tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing polyethylene glycol (macrogol), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and yellow ferric oxide.

5.1.2. Symtuza will be considered investigational in this study for those patients who are not virally suppressed at study entry.

5.2. Packaging and Labeling/Storage and Handling

5.2.1. SYMTUZA (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets are supplied as yellow to yellowish-brown, capsule-shaped, film-coated tablets debossed with "8121" on one side and "JG" on the other side. SYMTUZA is packaged in bottles of 30 tablets (NDC 59676-800-30), with a silica gel desiccant and child-resistant closure.

5.2.2. Study drug will be stored at 20°C-25°C (between 68°F-77°F); with excursions permitted to 15°C-30°C (59°F-86°F). • Dispensed in the original container. Container will be tightly closed with desiccant inside to protect from moisture.

5.3. Dosage and Administration

5.3.1. Study drug will be dosed as one tablet taken orally once daily with food in adults. For subjects who are unable to swallow the whole tablet, it may be split into two pieces using a tablet-cutter, and the entire dose should be consumed immediately after splitting.

5.4. Concomitant Medications

5.4.1. Contraindicated medications:

5.4.1.1. SYMTUZA® and the following drugs due to the potential for serious and/or life-threatening events or loss of therapeutic effect: alfuzosin, carbamazepine, cisapride, colchicine (in patients with renal and/or hepatic impairment), dronedarone, elbasvir/grazoprevir, ergot derivatives (such as: dihydroergotamine, ergotamine, methylergonovine), ivabradine, lomitapide, lovastatin, lurasidone, oral midazolam, naloxegol, phenobarbital, phenytoin, pimozide, ranolazine, rifampin, St. John's wort (Hypericum perforatum), sildenafil for pulmonary arterial hypertension, simvastatin, and triazolam.

5.4.2. Not recommended agents:

5.4.2.1. Rivaroxaban, esclicabazepine, oxcarbazepine, voriconazole, rifapentine, rifabutin, betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone, glecaprevir/pibrentasvir, simeprevir, everoliumus, irinotecan, salmeterol, avanafil, ticagrelor.

5.5. Accountability for Study Drug

5.5.1. Subjects will be instructed to bring all study medication in the original container at each clinic visit for drug accountability. The Investigator will be responsible for maintaining accurate records for all study drug bottles dispensed and tablets returned. Study medication supplies, including partially used or empty bottles, must be accounted for by the investigator prior to destruction of return.

5.5.2. The Investigator is responsible for ensuring adequate accountability of all used and unused study drug. This included acknowledgement of receipt of each shipment of study drug (quality and condition). All used and unused study drug dispensed to subjects must be returned to the site.

5.5.3. Study Drug accountability records will include:

5.5.3.1. Date received and quantity of IMP kits

5.5.3.2. Date, subject number, subject initials, the IMP kit number dispensed

5.5.3.3. Date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

5.6. Product Return or Disposal

5.6.1. Study drug return or disposal will be performed on site.

6. Study Design

6.1. Part 1

6.1.1. Methodology

6.1.1.1. Part I of the study is a Cohort Survey of HIV+ outpatient clinic patients currently receiving ART to assess medication adherence and tolerability.

6.1.2. Sample

6.1.2.1. Convenience sample of patients being seen in a single clinical site

6.1.2.2. Duration will be until enrollment of Part II has been completed

6.1.3. Eligibility criteria

6.1.3.1. Inclusion Criteria:

6.1.3.1.1. ≥ 18 years of age

6.1.3.1.2. HIV positive receiving ART of any type

6.1.3.2. Exclusion criteria

6.1.3.2.1. Inability to read/respond to questions written in English OR Spanish

6.1.4. Study Procedure

6.1.4.1. During patient triage, all patients who are HIV positive and currently prescribed anti-viral therapy will be offered participation in completing the Midland ART Adherence Survey (MAAS, Appendix 1). They will be provided a paper copy of the Study consent and the survey with a clipboard and a pen and allowed to self-complete it during the triage process. If they opt-in to the survey, they will turn in the completed surveys to staff members who will (1) determine if patient is eligible for Part II of study and (2) share the results with the provider, if subjects indicate they would like them shared. For those who opt out, no demographic data will be collected.

6.1.4.2. Survey sheets will not contain any Personal Identifying Information (PII). The results of the survey will be entered into a spreadsheet and analyzed at the completion of the enrollment period.

6.1.4.3. Subjects will be offered enrollment in Part 1 until target enrollment in part 2 has been completed or until subject sample population has been offered participation, whichever comes first.

6.2. Part 2

6.2.1. Methodology

6.2.1.1. Part 2 of the study is a prospective cohort analysis of change in adherence, tolerability and safety of subjects who reports poor adherence to ART due to intolerance/side effects from integrase inhibitor containing regimens when they are switched to DRV/COB/FTC/TAF and monitored for 4 months.

6.2.2. Sample

6.2.2.1. All subjects who meet pre-determined criteria from MAAS and meet other eligibility requirements will be offered enrollment into Part II of the study, the target enrollment is 30.

6.2.3. Eligibility Criteria

6.2.3.1. Inclusion Criteria

6.2.3.1.1. Meets inclusion criteria of part I of study

6.2.3.1.1.1. Currently on an integrase containing regimen AND

6.2.3.1.1.2. Reports non-adherent due to medication intolerance, defined by pre-determined criteria from Adherence Survey: [indicate a side effect to question 11 OR “yes” to questions 3 OR 7] AND [indicate missing more than 2 doses per month on question 8 OR 9 OR 10])

6.2.3.1.2. GFR≥30mL/min

6.2.3.1.3. AST/ALT ≤ 3 times upper limit of normal

6.2.3.1.4. Total bilirubin of ≤1.5 mg/dL

6.2.3.2. Exclusion Criteria

6.2.3.2.1. Known resistance to darunavir or tenofovir

6.2.3.2.2. Known intolerance to Symtuza or its components

6.2.3.2.3. Current pregnancy

6.2.3.2.4. Requires continued use of any of the agents in table 6.2.3.2.4

6.2.3.2.5. Cirrhosis, regardless of compensation status

6.2.3.2.6. Active, serious infections within 30 days of baseline

6.2.3.2.7. History of malignancy within 5 years of baseline, except cutaneous Kaposi’s sarcoma, basal cell or resected non-invasive cutaneous squamous cell carcinoma

6.2.3.2.8. Life expectancy of less than a year

6.2.3.2.9. Participation in any other investigation study 30 days prior to enrollment

Table 6.2.3.2.4 Contraindicated/not recommended Concomitant Medications

Alpha 1-Adrenoreceptor Antagonist	alfuzosin
Antiarrhythmics/Antianginals	amiodarone, dronedarone, ivabradine, lidocaine (systemic)
Anti-coagulants	apixaban,rivaroxaban,
Anti-convulsants	carbamezepine, phenobarbital, phenytoin, oxcarbazepine, esclicabazepine
Anti-gout	colchicine (in patients with renal and/or hepatic impairment)
Antimycobacterial	Rifampin, rifapentine, rifabutin
Ergot Derivatives	Such as: dihydroergotamine, ergonovine, ergotamine
Hepatitis C Virus Direct-Acting Antivirals	elbasvir/grazoprevir , glecaprevir/pibrentasvir, simeprevir
Herbal Products St.	John's wort (Hypericum perforatum)
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin
Other Lipid Modifying Agents	lomitapide
Inhaled Beta Agonist	salmeterol
Neuroleptics	lurasidone, pimozide
Opioid Antagonist	naloxegol
PDE-5 Inhibitor	sildenafil (for treatment of pulmonary arterial hypertension), avanafil
Platelet Aggregation Inhibitor	ticagrelor
Sedatives/Hypnotics	triazolam
Antiplatelet	ticagrelor
antineoplastic	Everoliumus, irinotecan
antifungals	voriconazole
Steroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone

6.2.4. Study Procedure

6.2.4.1. Overview

6.2.4.1.1. Subjects who are referred for screening from Part I who meet other eligibility criteria (see table 6.2.4.2.1) will be offered enrollment in Part 2. Those who provide consent will complete HIV Symptom Index (HIV-SI), a validated Patient Reported Outcome survey to assess side effects/quality of life, undergo physical and laboratory examinations, and ART will be switched to DRV/COB/FTC/TAF (Symtuza). For subjects who were not suppressed at their last lab evaluation, an HIV genotype will be performed prior to enrollment. Subjects who do not provide consent to enroll in the study will be referred back to their provider to address issues with tolerance and adherence.

6.2.4.1.2. Subjects will be followed for 16 weeks. During that period, they will be brought back for evaluation at the 4th and 16th week. At those evaluations, they will again complete the PRO and adherence surveys to assess tolerability and adherence. At the evaluations, they will also be monitored for safety and effectiveness via physical exams and laboratory studies. See Table 6.2.4.1.2

6.2.4.1.2.1. Labs at each visit: Complete Blood Count, Complete Metabolic Panel, Urinalysis, CD4 panel, HIV1 Quantitative viral load. If subject is of childbearing potential, urine pregnancy will be performed.

6.2.4.1.2.1.1. Special situations: If HIV viral load is >200 prior to baseline and not accompanied by recent genotype, a genotype will be performed.

6.2.4.1.3. Interim analysis will be performed when all subjects have completed 1 month evaluation or when 10 subjects have completed 4 month evaluation, whichever comes first.

6.2.4.2. Positive Screen

6.2.4.2.1. Subjects who screen positive from adherence survey defined as: (1)(indicate "yes" to questions 3 OR 7; or indicate a side effect to question 11) AND (2) (indicate missing more than 2 doses per month on question 8 OR 9 OR 10) will be offered enrollment in Part II.

Table 6.2.4.2.1 Positive Screen for Part 2

Positive screen for Part II one positive response in both columns:	
One from below	One from below
Question 3 = "Yes"	Question 8 = not "always" or "almost always"
Question 7 = "Yes"	Question 9 = greater than 2
Question 11 = "Side effect(s)" or named side effect	Question 10 = greater than 2

6.2.4.3. Screening Visit

6.2.4.3.1. At screening, written informed consent will be obtained; medical history of HIV-1 disease, current medications and medication history will be documented, any available HIV-1 resistance assays and hepatitis B immunity/viral loads will be documented, vitals (blood pressure, pulse, temperature, height and weight) from triage will be documented, physical exam will be performed.

6.2.4.3.2. After screening is performed, subjects will be allowed to either initiate baseline assessment or return within 45 days to do so.

6.2.4.4. Baseline Visit

6.2.4.4.1. If required labs have been performed within 30 days baseline may be performed same day and self-completed HIV Symptom Index (HIV-SI, Appendix 2) survey will be completed, baseline labs will be drawn and patient will be given 30 day supply of study drug.

6.2.4.4.2. If baseline is not done same day: vitals will be taken prior to HIV-SI survey being completed. Then updated history and symptom based physical will be performed and baseline labs will be drawn. Patient will be given 30 day supply of study drug; first dose will be taken in office.

6.2.4.5. Week 4 Visit

6.2.4.5.1. At 4 week visit, vitals will be taken, pill count will be performed, MAAS and HIV-SI surveys completed. Followed by history, symptom based physical, and laboratory exam. Patient will be given 90-day supply of study drug.

6.2.4.6. Week 14 Event

6.2.4.6.1. A script for commercial study drug will be sent to the patient's pharmacy of choice approximately 2 weeks prior to week 16 visit to ensure uninterrupted ART for the patient. Staff will confirm with patient that medication will be available to them via pharmacy prior to 16 week visit.

6.2.4.7. Week 16 Visit

6.2.4.7.1. At 16 week visit, subjects will have vitals taken, pill count will be performed; both the MAAS and HIV-SI will be completed, followed by history, symptom based physical, and laboratory exam. Pill count will be taken from bottle dispensed at baseline visit. Staff will confirm with patient that they have the commercial medication .

6.2.4.8. Early Discontinuation Visit

6.2.4.8.1. If the subject discontinues the study drug prior to the Week 16 Visit, the subject will be asked to return to the clinic within 10 days of stopping study drug for the Early Study Drug Discontinuation Visit. Every attempt should be made to keep the subject in the study and continue to perform the required follow ups and procedures through to the Week 16 Visit. If this is not acceptable to the subject or investigator, the subject may be withdrawn from the study. In the event that the subject is not kept in the study, physical and laboratory exam, as well as the MAAS and HIV-SI should be performed unless the subject does not consent to them.

6.2.4.9. Post Study Visit

6.2.4.9.1. If any significant abnormality is detected either at 4 month end of study visit or early discontinuation visit, a repeat exam and laboratories will be performed approximately 30 days following (or sooner, if PI believes to be clinically indicated) to ensure their resolution, unless at the determination of the PI they are deemed not related to the study drug.

Table 6.2.4.1.2: Overview of Study Procedures

Procedures	Screening and/or Baseline Combined Visit	Screening (if not same day as screen)	Baseline (if not same day as screen)	Week 4	Week 14 Event	Week 16	Early Discontinuation
Vitals	**X**	**X**	**X**	**X**		**X**	**X**
MAAS	**X**	**X**		**X**		**X**	**X**
HIV-SI	**X**		**X**	**X**		**X**	**X**
History and Physical	**X**	**X**					
History and Symptom based physical			**X**	**X**		**X**	**X**
Complete Blood Count	**X**		**X**	**X**		**X**	**X**
CD4 panel	**X**		**X**	**X**		**X**	**X**
Complete Metabolic Panel	**X**		**X**	**X**		**X**	**X**
HIV-1 Quantitative viral load	**X**		**X**	**X**		**X**	**X**
Urinalysis	**X**		**X**	**X**		**X**	**X**
Study Drug Dispensation			**X**	**X**			
Treatment Adherence and Accountability				**X**		**X**	
Commercial Script sent to Patient's Pharmacy					**X**		
HIV Genotype	if viral load >200 copies/mL at last check		if viral load >200 copies/mL at last check	if viral load >200 copies/mL at last check		if viral load >200 copies/mL at last check	if viral load >200 copies/mL at last check
Urine pregnancy	if indicated		if indicated	if indicated		if indicated	if indicated
Hepatitis B viral load	if indicated		if indicated	if indicated		if indicated	if indicated

7. Safety Data Collection and Reporting

7.1. See Appendix 3 (Exhibit B, Safety and Data Reporting)

7.2. Clinical Laboratory Abnormalities as Adverse Events

7.2.1.1. Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification or discontinuation must be recorded as an AE or SAE. In addition, laboratory or other abnormal assessments (e.g., EKG, x-rays, and vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis, not the laboratory result (i.e. "anemia," not "decreased hemoglobin").

7.3. Assessment of Adverse Events

7.3.1.1. The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity as well as for final review and confirmation of accuracy of event information and assessments.

7.4. Assessment of Causality for Study Drugs and Procedures

7.4.1.1. The investigator or qualified sub-investigator is responsible for assessing the relationship to the study drug using clinical judgement and the following considerations:

7.4.1.1.1. **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

7.4.1.1.2. **Yes**: There is reasonable possibility that the event may have been caused by the study drug.

7.4.1.2. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse reporting.

7.4.1.3. The relationship to study procedures (e.g., invasive procedures such as venipuncture) should be assessed using the following considerations:

7.4.1.3.1. **No**: Evidence exists that the adverse event has an etiology other than the study procedure.

7.4.1.3.2. **Yes**: The adverse event occurred as a result of protocol procedures.

7.5. Assessment of Severity

7.5.1.1. AE severity should be recorded and graded according to the Grading Scale for Severity of Adverse Events and laboratory Abnormalities (Appendix 4). For AE associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; which might not be in agreement with the grading of the laboratory abnormality.

7.5.1.2. The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; a severe reaction is not necessarily a serious reaction. For example, a subject might have a headache that is described as severe, but would not be considered a SAE unless it met one of the criteria for serious events.

7.6. Toxicity Management

7.6.1. All clinical events and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below.

7.6.1.1. Clinical events and clinically significant laboratory abnormalities will be graded according to the Grading Scale for Severity of Adverse Events and laboratory Abnormalities (Appendix 4).

7.6.1.2. Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 5 calendar days of receiving results and before study drug discontinuation, unless such a delay is not consistent with good medical practice.

7.6.1.3. Any questions regarding toxicity management should be directed to the Investigator.

7.6.2. Grades 1 and 2 Clinical Event or Laboratory Abnormality

7.6.2.1. Continue study drug at the discretion of the Investigator

7.6.3. Grade 3 Clinical Event or Laboratory Abnormality

7.6.3.1. For Grade 3 clinical event or clinically significant laboratory abnormality, study drug may be continued if the event is considered to be unrelated to study drug.

7.6.3.2. For a Grade 3 clinical event or clinically significant laboratory abnormality confirmed by repeat testing that is considered to be related to the study drug, study drug will be withheld until the toxicity returns to ≤ grade 2. When restarting study drug following resolution of the adverse event, the study drug should be restarted at full dose.

7.6.3.3. If following re-challenge with study drug a laboratory abnormality returns to ≥ Grade 3 and is considered to be related to the study drug, then the study drug will be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation.

7.6.4. Grade 4 Clinical Events or Laboratory Abnormality

7.6.4.1. For a Grade 4 clinical event or clinically significant laboratory abnormality confirmed by repeat testing that is considered to be related to the study drug, the study drug will be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first.

7.6.4.2. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

7.6.4.3. Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., elevated CK after significant exercise or triglyceride elevation on a non-fasting specimen) or a clinical event considered unrelated to the study drug, but must be discussed with the Investigator.

7.6.5. ALT Flare

7.6.5.1. Defined as: serum ALT > 10 x upper limit of normal (ULN) and > 2 times baseline value, confirmed with repeat testing within 7 days of original results receipt, with or without associated symptoms

7.6.5.2. Management of ALT Flare

7.6.5.2.1. When initial results are received, schedule subject to return to the clinic as soon as possible (ideally within 3 days of initial blood draw). During the visit, in addition to redrawing blood for repeat CMP testing, clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.

7.6.5.2.2. If ALT elevation is confirmed, the following labs should be performed: plasma HBV DNA, HBV serology (HBsAg and HBsAb), HAC IgM, HCV serology, quantitative HDV RNA.

7.6.5.2.3. Based on the results of the confirmatory tests, the following treatment modifications are recommended:

7.6.5.2.3.1. Elevated liver enzymes, normal or stable total bilirubin relative to baseline

7.6.5.2.3.1.1. If ALT levels are elevated (as specified in 7.7.5.1) with normal or stable total bilirubin, the subject may remain on the study drug and should be monitored weekly until ALT levels return to normal or Baseline level. During monitoring, if the ALT values remain persistently elevated, the Investigator will determine whether the study drug should be discontinued.

7.6.5.2.3.2. Elevated liver enzymes, elevated total bilirubin

7.6.5.2.3.2.1. If ALT levels are elevated (as specified in 7.7.5.1) and total bilirubin is confirmed to be ≥ 2 x Day 1 value and is > ULN, the investigator should

consider discontinuing the study drug. The subject should be monitored weekly until ALT and total bilirubin levels return to normal or Day 1 level.

7.6.5.2.3.3. During monitoring, if the ALT values and the liver function tests remain persistently elevated, the Investigator should consider discontinuing the study drug.

7.6.6. Management of Potential Hepatobiliary Toxicity

7.6.6.1. Any subject exhibiting signs/symptoms or laboratory abnormalities suggestive of possible hepatobiliary toxicity should undergo thorough examination and clinical workup as deemed appropriate by the Investigator. Consideration should be given to appropriate imaging studies (e.g., ultrasound of the liver and biliary tree) and potential consultation with a gastroenterologist with specialty training in hepatobiliary diseases.

7.7. Criteria for discontinuation of study drug

7.7.1. In the event of the following, study drug will be discontinued: unacceptable toxicity, subject request for any reason, pregnancy, development of active tuberculosis, discontinue of the study at the request of the IRB

7.7.2. In the event of the following, study drug may be discontinued: in the event of significant new illness that compromises the ability to assess end points, lack of efficacy, subject noncompliance.

7.7.3. In the event that study drug is discontinued, every attempt should be made to keep the subject in the study and continue to perform the required follow ups and procedures through to the Week 16 Visit

7.8. **Management of viral rebound**

7.8.1. At any post baseline visit either (1) an HIV-1 RNA ≥ 50 copies/mL for subjects who were <50 at baseline or (2) an increase by 1 log for subjects who were ≥ 50 copies at baseline, will be repeated for confirmation within 4 weeks of the original test result. If confirmatory testing is ≥ 200, HIV-1 genotype will be performed on the confirmatory sample. Subject may be withdrawn from the study at investigators discretion if resistance suggested by results. If no resistance is found, repeat viral load should be repeated again 4 weeks later.

8. Statistical Considerations

8.1. Statistical and Analytic Plans

8.1.1. All statistical methods will be based on the International Conference on Harmonization (ICH) E9 document “Statistical Principles for Clinical Trials”.

8.2. Hypotheses –

8.2.1. Part 1 is exploratory

8.2.1.1. Primary Endpoint

8.2.1.1.1. Percentage of subjects reporting suboptimal adherence to ART therapy on the MAAS. Optimal adherence is measured as a score of 90% or better on Rasch score.

8.2.1.2. Secondary Endpoints

8.2.1.2.1. To assess the psychometric properties of the Midland ART Adherence Survey. We will employ a Rasch statistical approach. Rasch Analysis (RA) is a unique approach of mathematical modeling based upon a latent trait and accomplishes stochastic (probabilistic) conjoint additivity (conjoint means measurement of persons and items on the same scale and additivity is the equal-interval property of the scale).

8.2.1.2.2. Identify and classify the case mix or heterogeneity of subjects who report suboptimal and optimal adherence. Optimal adherence is measured as a Rasch score of better than

90% on the Midland AD Adherence scale. Suboptimal is any score 90% or below. Rasch scores range from 0% (no adherence) to 100% (perfect adherence).

8.2.2. Part 2

8.2.2.1. Primary Endpoint

8.2.2.1.1. Percentage of subjects reporting suboptimal adherence, analyzed by intention to treat, from baseline to 16 weeks.

8.2.2.1.1.1. We hypothesize that a minimum of 85% of subjects taking DRV/COB/FTC/TAF will demonstrate an optimal adherence score from baseline to four-months as measured by the Midland ART Adherence Survey. Optimal adherence is defined as a Rasch score greater than or equal to 90%. Rasch scores range from 0% (no adherence) to 100% - (perfect adherence).

8.2.2.2. Secondary Endpoints. These are descriptive endpoints so no hypotheses are tested.

8.2.2.2.1. Change at 4 months from baseline in tolerability measured by standardized patient reported outcome questionnaire

8.2.2.2.2. Percentage of subjects with greater than or equal to 90% by pill count

8.2.2.2.3. Proportion of subjects that have HIV-1 RNA ≥ 50 copies/mL at baseline and at month 4

8.2.2.2.4. Proportion of subjects with significant changes at 4 months from baseline in serum creatinine, AST or ALT

8.2.2.2.5. Change at 4 months from baseline in absolute and percentage CD4.

8.2.2.2.6. Change at 4 months from baseline in weight

8.2.2.2.7. Number of drug discontinuation for any reason

8.3. Analysis Datasets

8.3.1. Demographic:

8.3.1.1. This dataset contains all subjects' demographic data (i.e., Age, Race, and Gender), disposition data (i.e., Date patient withdrew from the study), and key dates such as date of first dose, date of last collected Case Report Form (CRF) and duration on treatment. The dataset has the format of one observation per subject.

8.3.2. Laboratory:

8.3.2.1. This dataset contains all subjects' laboratory data, in the format of one observation per subject per test code per visit per accession number. Here, we derive the study visits according to the study window defined in the SAP, as well as re-grade the laboratory toxicity per protocol. If the laboratory data are collected from multiple local lab centers, this analysis dataset will also centralize the laboratory data and standardize measurement units by using conversion factors.

8.3.3. Intent-to-Treat:

8.3.3.1. This dataset contains derived primary and secondary endpoint variables from all subjects initially enrolled in the study. This dataset has the format of one record per subject per analysis period.

8.3.4. Modified-Intent-to-Treat:

8.3.4.1. This dataset contains derived primary and secondary endpoint variables from all subjects who took one dose of the treatment medications. This dataset has the format of one record per subject per analysis period.

8.3.5. Vital Sign:

8.3.5.1. This dataset contains all subjects' vital signs collected during the trial. This dataset has the format of one observation per subject per vital sign per visit, similar to the structure for the laboratory analysis dataset.

8.3.6. Adverse Event:

8.3.6.1. This dataset contains all adverse events (AEs) reported including serious adverse events (SAEs) for all subjects. A treatment emergent flag, as well as a flag to indicate if an event is reported within 30 days after the subject permanently discontinued from the study, will be calculated. This dataset has a format of one record per subject per adverse event per start date.

8.3.7. Medication:

8.3.7.1. This dataset contains the subjects' medication records including concomitant medications and other medications taken either prior to the beginning of study or during the study. This dataset has a format of one record per subject per medication taken per start date. Incomplete and missing medication start or stop dates will be imputed using instructions defined in the SAP.

8.3.8. Safety:

8.3.8.1. This dataset contains data with one record per subject per analysis period to capture safety parameters for all subjects.

8.4. Description of Statistical Methods

8.4.1. General Approach

8.4.1.1. When a trial is designed so that more than one study endpoint or comparison could lead to a conclusion that effectiveness was established, testing each endpoint separately at alpha 0.05 will inflate the Type I error rate and overstate the statistical significance. Therefore, we will use the primary endpoint from Part 2 as our measure at the 0.05 level to reduce the potential for a Type I error rate.

8.4.1.2. After the data have been cleaned, we will examine the distribution and dispersion of data through descriptive numerical summaries and graphical tools such as scatter plots and box plots, probability plots, scatter matrix plots, co-plots, and trellis graphics to assess distributional assumptions and relationships among important variables. Before attempting a longitudinal analysis of the change in our outcomes using a mixed, generalized linear model, we will use profile plots, empirical summary plots and correlograms to guide us in the formulation of our model.

8.4.1.3. All data will be summarized. For baseline characteristics and safety outputs a total overall column will be included to summarize all subjects. Where appropriate, data will be summarized by visit. In summary tables of continuous variables, the minimum and maximum statistics will be presented to the same number of decimal places as the original data. The arithmetic mean (AM), median, 95% confidence interval (CI), standard deviation (SD) and standard error (SE) will be presented to one more decimal place than the original data.

8.4.1.4. In summary tables of categorical variables, counts and percentages will be used. In non-parametric summaries and analyses the minimum and maximum will be presented to the same number of decimal places as the original data. The mean, median, lower and upper quartiles will be presented to one more decimal place than the original data. The median difference and 95% CI will only be presented in statistical analysis outputs.

8.4.1.5. Preliminary analyses will examine descriptive and clinical characteristics at baseline. Stata (Version 16.1) and R (version 3.6.0) statistical packages will be used for all data analysis.

8.5. Part 1 –

8.5.1. Analysis of Primary End-Point

8.5.1.1. The dependent variable is measured on an ordinal scale (Midland ART Adherence Survey). However, employing Rasch analysis we will convert the data to a standardized range from 0 to 100, where 100 is perfect adherence and zero (0) is complete failure to adhere. Using this scale we will examine the proportion of subjects who meet or exceed 90% adherence.

8.5.2. Analysis of Secondary End-Points

8.5.2.1. To assess the psychometric properties of the Midland ART Adherence Survey, we will employ six criteria used in the Rasch approach to evaluating rating scale effectiveness. First, a minimum of 10 observations should be in each category. Second, the shapes of the probability curves should be peaked for each category. Third, the average category measures should increase with the rating scale categories. Fourth, the OUTFIT mean square statistics should be less than 1. Fifth, threshold calibrations should increase with rating scale category. Sixth, the category thresholds should be at least 1.4 logits apart and no more than 5 logits apart.

8.5.2.2. Identify and classify the case mix or heterogeneity of subjects who report suboptimal adherence we will use latent class analysis (LCA); which allows us to identify a finite number of latent subgroups and to explore how treatment effect varies across these subgroups. Such person-centered approaches transcend limitations imposed by diagnostic categories and

classify subjects into latent homogenous classes based on similar response patterns. Latent subgroups of subjects are compared with reference to shape (qualitative differences) symptom levels (quantitative differences).

8.6. Part 2 –

8.6.1. Primary Endpoint

8.6.1.1. Percentage of subjects reporting suboptimal adherence, analyzed by intention to treat, from baseline to four-months using Rasch scores. The hypothesis testing will be carried out at the 5% (2-sided) significance level unless otherwise specified. P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.

8.6.1.2. We hypothesize that a minimum of 85% of subjects taking DRV/COB/FTC/TAF will demonstrate optimal adherence from baseline to four-months as measured by the Midland ART Adherence Survey. Optimal adherence is defined as a Rasch score greater than or equal to 90%. Rasch scores range from 0% (no adherence) to 100% (perfect adherence).

8.7. Part 2 - Analysis of Secondary End-Points

8.7.1. These are descriptive endpoints so no hypotheses are tested.

8.7.1.1. Change at 4 months from baseline in tolerability measured by standardized patient reported outcome questionnaire.

8.7.1.2. Percentage of subjects with greater than or equal to 90% by pill count

8.7.1.3. Proportion of subjects that have HIV-1 RNA ≥ 50 copies/mL at baseline and at month 4

8.7.1.4. Proportion of subjects with significant changes at 4 months from baseline in serum creatinine, AST or ALT

8.7.1.5. Change at 4 months from baseline in absolute and percentage CD4.

8.7.1.6. Change at 4 months from baseline in absolute and percentage weight

8.7.1.7. Number of drug discontinuation for any reason

8.7.2. All data will be summarized. For baseline characteristics and safety outputs a total overall column will be included to summarize all subjects. Data will be summarized by visit. In summary tables of continuous variables, the arithmetic mean (AM), median, 95% confidence interval (CI), standard deviation (SD) and standard error (SE) will be presented to one more decimal place than the original data. In summary tables of categorical variables, counts and percentages will be used.

8.7.3. We will identify and classify the case mix or heterogeneity of subjects adherence we will using latent class analysis (LCA); which allows us to identify a finite number of latent subgroups and to explore how treatment effect varies across these subgroups. Using the clinical, psychosocial and demographic variables we will classify subjects into latent homogenous classes based on similar response patterns.

8.7.4. Using the latent classes identified above we will use class membership (latent class) in a as a predictor of a distal standardized outcome adherence range from 0 to 100.

8.8. Sample

8.8.1. All subjects who meet pre-determined criteria from Adherence Survey and meet other eligibility requirements will be offered enrollment into Part II of the study. As Part 1 of the study is tied to Part 2, we will employ the same sampling formulation for minimum sample size.

8.8.2. We follow the work of Viechtbauer et al (2015) to calculate sample size. For encountering a reduction in primary-end-points of 10%, with a 95% confidence interval we use the formula $n=\ln(1-0.95)/\ln(1-0.10)=30$ subjects are needed. This will ensure that we will encounter at least one reduction of the primary end-point at a 95% confidence level.

9. Responsibilities

9.1. Good Clinical Practice

9.1.1. The rights and welfare of the individual clinical research subject must always be the paramount consideration in conducting clinical research. Accordingly, clinical research must be conducted in a manner that protects the rights, welfare and confidentiality of the human subject and also assures data credibility by protecting the integrity of accurate data that has been demonstrably collected according to the approved protocol.

9.2. Investigator Responsibilities

9.2.1. The Investigator is responsible for:

9.2.1.1. Ensuring that the study is conducted according to the signed investigator statement/agreement, the investigational plan (study protocol), applicable regulations

9.2.1.2. Ensuring that all persons assisting with the trial are adequately informed about the protocol, the study drug, their trial-related duties and functions

9.2.1.3. Protection of the rights, safety, and welfare of subjects under the investigator's care

9.2.1.4. Control of the study drug included in the investigation.

9.2.1.5. Assuring that each subject's informed consent is obtained appropriately

9.2.1.6. Proper delegation of authority for the conduct of various aspects of the study so that the investigator retains control and knowledge of the study

9.3. Control of Study Drug

9.3.1. The investigator shall control the study drug. The Investigator is responsible to ensure that:

9.3.1.1. The study drug is administered only to subjects under the investigator's personal supervision or under the supervision of a qualified sub-investigator responsible to the investigator.

9.3.1.2. The study drug is not to be supplied/provided to any person not authorized to receive it.

9.3.1.3. Adequate records of the disposition of the study drug are maintained, including dates, quantity, receipt, distribution to subjects, and disposition.

9.4. Medical Decision Making

9.4.1. Primary Investigator or sub-investigator must be designated as responsible for all trial-related medical decisions. Medical decisions must be made by a qualified person permitted by state licensure laws to make or enact such decisions. The investigator should:

9.4.2. Ensure that adequate medical care is provided to a subject for any adverse events related to the trial, during and as follow-up to a subject's participation.

9.4.3. Inform a subject when medical care is needed for intercurrent illness (es) of which the investigator/sub-investigator becomes aware.

9.4.4. Inform the subject's primary physician about the subject's participation in the trial if the subject agrees to the primary physician being informed, and has signed a HIPAA Authorization form permitting such disclosure.

9.5. IRB/IEC Review and Approval

9.5.1. The investigator shall assure that initial and continuing review of the proposed clinical study is performed according to the policies and procedures of the Central Institutional Review Board (IRB), as well as with any other IRB that has jurisdiction.

9.5.2. Continuous approval from the IRB must be maintained.

9.5.3. All unanticipated problems involving risk to human subjects or others are promptly reported to the IRB. All serious adverse events are reported to the IRB within twenty-four hours of time investigator is aware of the event.

9.5.4. Any changes in the research activity are promptly reported to the IRB.

9.5.5. No changes are made in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

9.6. Informed Consent

9.6.1. The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study related procedures. The investigator must use the most current IRB/IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements. The consent form will inform subjects about sample retention.

9.7. Confidentiality

9.7.1. The investigator will assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. All information and data will be collected by the investigator. All collected data concerning participants or their participation in this study will be considered confidential and maintained in a HIPAA-compliant electronic medical recording system. Subject data pertinent to the study will be de-identified and access limited only to personnel directly involved in this research study. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the participant. Study data will not be transmitted nor disclosed to a third-party. Paper records will be kept in secure files and electronic records will be password protected.

9.8. Study Files and Retention of Records

9.8.1. The investigator shall keep and maintain adequate and accurate records, including:

9.8.2. Case histories on each individual study subject that record all observations and other data pertinent to the investigation

9.8.3. Screening, enrollment, and informed consent documentation; demonstrating that informed consent was obtained prior to participation in the study

9.8.4. Study reports, including reports of progress, safety, financial disclosure and final completion

9.9. Records retention

9.9.1. Midland Research Group Inc. will use on-site facility and if storage becomes unavailable due to capacity of documents, then Midland Research Group Inc will use an offsite facility.

9.9.2. FDA regulation requires an investigator to retain records a minimum of two years after the close of the study or after the records are no longer required to support a drug or marketing application, whichever is longer.

9.9.3. Contract commitments must be met.

9.9.4. Record transfer or record destruction should be verified and documented.

9.10. Case Report Forms

9.10.1. For each subject consented, a study file will be completed by an authorized study staff member who has completed training for this function. The study file will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment should be completed only after all data related to eligibility have been received. Subsequent to data entry, a second staff member will perform source data verification.

9.11. Study Drug Accountability and Return

9.11.1. Unused study drug supplies will be destroyed. Investigator will assist with disposal procedures and provide appropriate instruction for destruction of unused study drug supplies.

9.12. Protocol Compliance

9.12.1. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.13. Sponsor Responsibilities

9.14. Protocol Modifications

9.14.1. Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Investigator, who must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.15. Study Report and Publications

9.15.1. The Investigator is responsible for submitting any reports within time periods and according to procedures called for by:

9.15.1.1. Midland Research Group Inc . or applicable division or departmental policy or procedures, including the Institutional Review Board (IRB)

9.15.1.2. Contractual agreements with collaborators, etc.

9.16. Payment Reporting

9.16.1. Investigators and their study staff may be asked to provide services performed under this protocol. If required under applicable statutory and regulatory requirements, Midland Research Group Inc. will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.17. **Access to Information for Monitoring, Auditing or Inspection**

9.17.1. As per contract

9.18. Study Discontinuation

9.18.1. The investigator reserves the right to terminate the study at any time. Should this be necessary, they will arrange discontinuation procedures and notify the appropriate regulatory authorities and the IRB. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

9.19. PUBLICATIONS

9.19.1. As per contract

References

1) Ortego C, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS and Behavior. 2011;15:1381–1396. doi: 10.1007/s10461-011-9942-x.
2) Robbins RN, Spector AY, Mellins CA, Remien RH. Optimizing ART Adherence: Update for HIV Treatment and Prevention. *Current HIV/AIDS reports*. 2014;11(4):423-433. doi:10.1007/s11904-014-0229-5.
3) Orkin C, Molina JM, Negredo N, et al; EMERALD Study Group. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomized, non-inferiority trial. Lancet HIV. 2018 Jan;5(1):e23-e34.

APPENDIX 1: Midland ART Adherence Survey (MAAS)

Midland ART Adherence Survey Survey #_____

Age: ☐ 18-35 ☐36-49 ☐ 50-65 ☐ 66-99 Ethnicity: _____ Gender: _____

How long on ART? ☐ <1 year ☐ 1-5 years ☐ 6-10 years ☐ 11-15 years ☐ 16 or more years

1. Do you sometimes forget to take your HIV medications? ☐ Yes ☐ No

3. Have you ever not taken your meds because you felt worse when you took it? ☐ Yes ☐ No

4. When you travel or leave home, do you sometimes forget to bring along your medications? ☐ Yes ☐ No

5. Did you take your HIV medicine yesterday? ☐ Yes ☐ No

6. When you feel like your health is good, do you sometimes stop taking your medicine? ☐ Yes ☐ No

7. Do you ever miss doses of your medications because of side effects from them? If so, what side effects? ☐ Yes ☐ No

_____

Current prescribed HIV regimen:

- ☐ Biktarvy
- ☐ Genvoya
- ☐ Julica
- ☐ Triumeq
- ☐ Isentress/Isentress HD
- ☐ Stribild
- ☐ Dulera
- ☐ Tivicay
- ☐ Symtuza
- ☐ Atripla
- ☐ Complera
- ☐ Odefsey
- ☐ Reyataz or Evotaz
- ☐ Prezista or Prezcobix
- ☐ Descovy
- ☐ Truvada
- ☐ Epzicom
- ☐ Edurant
- ☐ Intelence
- ☐ Sustiva
- ☐ Selzentry

8. How often do you take your HIV medications?

- ☐ ALWAYS –never miss a dose
- ☐ ALMOST ALWAYS-miss 1-2 times a month
- ☐ USUALLY-miss 3- 5 times a month
- ☐ SOMETIMES-miss more than 5 times, but take more than 5 times a month
- ☐ RARELY-take 3- 5 times a month
- ☐ ALMOST NEVER-take 1-2 times a month
- ☐ NEVER-do not take the medication

9. How many days in the last week did you not take your HIV medication? _____

10. How many days in the last month did you not take your HIV medication? _____

11. What is your biggest issue with being able to take your medication: _____

We are looking at some ways to help our patients with their medications. Would it be ok to share your responses with your provider if we think we might have some options for you? ☐ Yes ☐ No

APPENDIX 2: Self-Completed HIV Symptom Index (HIV-SI)

Self-completed HIV Symptom Index[15]

INSTRUCTIONS: The following questions ask about symptoms you might have had during the **past four weeks**. Please answer the following questions by placing a checkmark in the appropriate box.

Symptom	Did not have this symptom	Symptom did not bother me	Symptom bothers me a little	Symptom bothers me	Symptom bothers me a lot
Fatigue or loss of energy					
Fevers, chills or sweats					
Feeling dizzy or lightheaded					
Pain, numbness or tingling in the hands or feet					
Trouble remembering					
Nausea or vomiting					
Diarrhea or loose bowel movements					
Felt sad, down, or depressed					
Felt nervous or anxious					
Difficulty falling or staying asleep					
Skin problems, such as rash, dryness or itching					
Cough or trouble catching your breath					
Headache					
Loss of appetite or a change in the taste of food					
Bloating, pain, or gas in your stomach					
Muscle aches or joint pain					
Problems with having sex, such as loss of interest or lack of satisfaction					
Changes in the way your body looks such as fat deposits or weight gain					
Problems with weight loss or wasting					
Hair loss or changes in the way your hair looks					

EXHIBIT B

Requirements for Safety Data Collection and Reporting

1. OVERVIEW

As the sponsor of the Study, INSTITUTION and PRINCIPAL INVESTIGATOR shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this EXHIBIT, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The INSTITUTION and PRINCIPAL INVESTIGATOR will provide safety information to the COMPANY on adverse events, special situations including pregnancies and product quality complaints as defined within this EXHIBIT.

2. Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events, special situations including pregnancies and product quality complaints will be reported as described in this exhibit from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of a product under study within the study.

For the purposes of this study, the J&J medicinal product is: Symtuza

3. Definitions

3.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])
This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

3.2. Adverse Events of Special Interest

Adverse events of special interest are events that the COMPANY is actively monitoring as a result of a previously identified signal (even if non-serious). No adverse events of special interest will be collected for this study.

3.3. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a J&J medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected J&J medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset

- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- J&J protocol ID

3.4. Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

3.5. Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

3.5.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization

was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

3.5.2. Life-Threatening Conditions

The cause of death of a subject in a study 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

4. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information. https://www.symtuza.com/

5. Special Reporting Situations

Safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product
- Inadvertent or accidental exposure to a J&J medicinal product
- Medication error (includes potential, intercepted or actual) involving a J&J product (with or without patient exposure to the J&J Product(s) Under Study, e.g., name confusion)
-
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a J&J medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a J&J medicinal product

These safety events may not meet the definition of an adverse event; however, from a COMPANY perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of becoming aware of the event.**

6. Pregnancy

All initial reports of pregnancy must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the J&J medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a J&J medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION and PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at the COMPANY's request.

8. Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for J&J Medicinal Products to the COMPANY

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a J&J medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a J&J medicinal product.

All (serious and non-serious) adverse events reported for a J&J medicinal product should be followed-up in accordance with clinical practice.

8.1. SAEs, Adverse Events of Special Interest and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The INSTITUTION and the PRINCIPAL INVESTIGATOR) will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a J&J product under study in a form provided by the COMPANY in accordance with Section 9, Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to COMPANY.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, to the COMPANY using the COMPANY's Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, Adverse Events of Special Interest, serious ADR or special situation is required.

- The INSTITUTION and/or PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant extraordinary (not including routine initial or follow-up ICSR submission) correspondences with regulatory authorities and ethics committees regarding any and all serious adverse irrespective of association with the J&J Product under study, are to be provided to the COMPANY using a transmission method in Section 9 within **24 hours of such report or correspondence being sent to applicable health authorities.**

8.2. Non-Serious AEs

All non-serious adverse events should be reported to COMPANY according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

8.3. PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the COMPANY, and are mandated by regulatory agencies worldwide. The COMPANY has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a J&J medicinal product under study must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The J&J contact will provide additional information/form to be completed.

If the defect for a J&J medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

9. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-J&J Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-J&J medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

10. Transmission Methods

The following methods are acceptable for transmission of safety information to the COMPANY:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by the COMPANY.

11. SAEs Listing

At a minimum, on a semi-annual basis and at the end of the Study, COMPANY will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to the COMPANY. SPONSOR and/or PRINCIPAL INVESTIGATOR will review this listing and will resolve any discrepancies with the data provided by the COMPANY.

12. Dissemination of Safety Information from COMPANY to INSTITUTION/PRINCIPAL INVESTIGATORS

PRINCIPAL INVESTIGATOR will be responsible for submitting IND safety reports for the Study Product to INSTITUTION's IRB in accordance with Federal regulations 21 CFR 312.66. The PRINCIPAL INVESTIGATOR will provide a copy of each IND safety report to sub-investigators where the study design is either a multi-center or cooperative study.

COMPANY agrees to provide to the PRINCIPAL INVESTIGATOR IND safety reports for the J&J Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

13. Contacting COMPANY Regarding Safety

The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by the COMPANY.

APPENDIX 4 GRADING SCALE FOR SEVERITY OF ADVERSE EVENTS AND LABORATORY ABNORMALITIES

Laboratory Tests	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	8.5-10.0	7.5-8.49	6.5-7.49	<6.5
ANC	1000-1300	750-999	500-749	<500
Platelets	100-125	50-99	25-49	<25
WBC	2.0-2.5	1.5-1.99	1.0-1.49	<1
Hyponatremia	>130	125-129	121-124	<121
Hypernatremia	<150	150-154	154-159	>159
Hypokalemia	>3	2.5-3.0	2.0-2.49	<2.0
Hyperkalemia	5.6-6.0	6.01-6.5	6.51-7.0	>7.0
Hypoglycemia	55-64	40-54.9	30-39.9	<30
Hyperglycemia, Fasting	110-125	126-250	251-500	>500
Hypocalcemia (corrected)	Below normal but above 7.8	7.0-7.8	6.1-6.9	<6.1
Hypercalcemia (corrected)	Above normal but below 11.5	11.5-12.5	12.6-13.5	>13.5
Total Bilirubin	Up to 1.5 ULN	1.5-2.5 x ULN	2.5-5.0 x ULN	>5.0 x ULN
BUN	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
Creatinine	1.5-2.0	2.01-3.00	3.01-6.00	>6.00
Bicarb	16-LLN	11-15.9	8-10.9	<8.0
Triglycerides (fasting)	NA	500-750	751-1200	>1200
LDL (fasting)	130-160	161-190	>190	NA
CK	3-6 x ULN	6.1-10 x ULN	10.1-20 ULN	>20 x ULN
AST	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
ALT	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
GGT	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
Alk Phos	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
Lipase	1.0-1.5 x ULN	1.51-3.0 x ULN	3.01-5.0 x ULN	>5.0 x ULN
Albumin	NA	2.0 to <LLN	<2.0	NA
Hematuria	>ULN-10	>10-75	>75	NA
Proteinuria	1+	2-3+	4+	NA
Glycosuria	1+	2-3+	4+	NA
Cardiac Arrhythmia	Asymptomatic and no intervention indicated	Asymptomatic and non-urgent intervention indicated	Symptomatic and non-urgent intervention indicated	Life threatening or urgent intervention indicated
Cardiac ischemia/infarct	NA	NA	Stable angina or testing with ischemia	Unstable angina or acute MI
Hemorrhage	NA	Symptomatic, no transfusion indicated	Symptomatic, ≤ 2 units PRBC's transfusion indicated	Life threatening or > 2 units PRBC's transfusion indicated
Hypertension	Systolic: 140-159 Diastolic: 90-99	Systolic: 160-179 Diastolic: 100-109	Systolic: >179 Diastolic: 110	Life threatening (i.e. malignant hypertension) or requiring hospital admission
Hypotension	NA	Symptomatic, corrected with oral fluids	Symptomatic, IV fluids indicated	Refractory shock

APPENDIX 4: Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Pericardial effusion	Asymptomatic, small	Asymptomatic, mod-large	Physiologic consequences, no urgent intervention indicated	Physiologic consequences, urgent intervention indicated
PR prolongation	0.21-.025	>0.25	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	450-470 Or increase <30 above baseline	471-499 Or increase 30-50 above baseline	>499 Or increase >50 above baseline	Life threatening dysrhythmia
Thrombus	NA	DVT, no intervention or anticoagulation indicated	DVT, intervention or anticoagulation indicated	PE or life-threatening embolism
Vasovagal episode	No LOC	LOC	NA	NA
Ventricular dysfunction	NA	Asymptomatic and intervention indicated	New/worsening symptomatic CHF	Life threatening CHF
Bronchospasm	FEV1 70-80%	FEV1 50-69%	FEV1 25-49%	FEV1<25%, cyanosis or intubation
Dyspnea	On exertion, minimal, without impact on activities	On exertion, moderate, with impact on activities	At rest, unable to perform typical activities	Resp failure with vent support indicated
Uveitis	Asymptomatic	Symptomatic or intervention indicated	Posterior or pan-uveitis or operation indicated	Disabling visual loss
Visual changes from baseline	minimal, without impact on activities	moderate, with impact on activities	unable to perform typical activities	Disabling visual loss
Alopecia	Thinning detectable by subject	Thinning/patchy hair loss detectable by provider	Complete hair loss	NA
Rash	Localized macular rash	Diffuse rash or target lesions; no vesicles, bulla or ulceration. No mucosal involvement	Diffuse rash or target lesions; with vesicles, few bulla or superficial ulceration. mucosal involvement of one site	Extensive bullous lesions/more than one site of mucosal involvement, Stevens-Johnson syndrome or toxic epidermal necrolysis
Pigmentation changes	Slight or localized	Marked or generalized	NA	NA
Pruritis	minimal, without impact on activities	moderate, with impact on activities	Severe, unable to perform typical activities	NA
Anorexia	Mild, not decreasing intake	Decreased intake, no significant weight loss	Significant weight loss	Aggressive intervention indicated (i.e. feeding tube) or life threatening
Ascites	Asymptomatic	Symptomatic, Intervention indicated	Symptomatic despite intervention	Life threatening consequences

APPENDIX 4: Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Cholecystitis	NA	Medical intervention indicated	Procedure indicated	Life threatening consequences (sepsis/perforation)
Constipation	NA	Persistent, requiring regular use of diet modification, laxatives/enemas	Obstipation with manual evacuation indicated	Life threatening consequences (obstruction)
Diarrhea	Transient/ intermittent or increase of >3 stools over baseline/24 hr.	Persistent or increase of 4-6 stools over baseline/24 hr.	Bloody diarrhea or increase of >6 stools over baseline/24 hr.	Life threatening consequences (shock)
Dysphagia	Able to eat usual diet	Causes alteration of diet, but no medical intervention indicated	Causes severe alteration of diet, medical intervention indicated	Life threatening reduction of oral intake
Mucositis/stomatitis	Erythema	Patchy Ulcerations or pseudomembranous	Confluent Ulcerations or pseudomembranous or mucosal bleeding	Tissue necrosis or diffuse mucosal bleeding or life threatening consequences
Nausea	Transient or intermittent	Persistent resulting in decreased oral intake 24-48 hours	Persistent resulting in minimal oral intake >48 hours or aggressive rehydration indicated	Life threatening consequences
Pancreatitis	NA	Symptomatic, no hospitalization indicated	Symptomatic, hospitalization indicated	Life threatening consequences
Proctitis	Discomfort	Minimal interference with usual activities or medical intervention indicated	Unable to perfume usual activities or operative intervention indicated	Life threatening consequences
Vomiting	Transient or intermittent	Persistent resulting in decreased oral intake 24-48 hours	Persistent resulting in minimal oral intake >48 hours or aggressive rehydration indicated	Life threatening consequences
Psychiatric issues (i.e. anxiety, agitation, depression, mania, psychosis)	minimal, without impact on activities	moderate, with impact on activities	Severe, unable to perform typical activities	Behavior potentially harmful to self/others or unable to perform self-care
AMS	minimal, without impact on activities	lethargy, with impact on activities	Confusion, memory impairment lethargy, or somnolence, unable to perform typical activities	Delirium/obtundation or coma
Ataxia	Minimal but detectable on exam, without impact on activities	moderate, with impact on activities	marked, unable to perform typical activities	Disabling causing inability to care for self

APPENDIX 4: Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Cognitive and behavior (including dementia and ADD)	Minimal, without impact on activities. No special resourced indicated	moderate, with impact on activities or part-time special resourced indicated	marked, unable to perform typical activities or full-time special resourced indicated	Disabling causing inability to care for self or institutionalization
CNS Ischemia	NA	NA	Transient ischemic attach	CVA/stroke with neurological deficit
Headache	Minimal but detectable on exam, without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or hospitalization indicated
Insomnia	NA	moderate, with impact on activities or part-time special resourced indicated	marked, unable to perform typical activities or full-time special resourced indicated	Disabling causing inability to care for self
Neuromuscular Weakness	Asymptomatic but detectable on exam, without or minimal impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Sensory alteration	Asymptomatic but detectable on exam, without or minimal impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Seizure, new onset	NA	1 seizure	2-4 seizures	Prolonged or repetitive seizures or difficult to control
Seizure, pre-existing	NA	Increased frequency, no change in character	Change from baseline in either duration or quality	Prolonged or repetitive seizures or difficult to control
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Arthralgia	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Bone Mineral Loss	BMP t-score or z-score -2.5 to -1.3	BMP t-score or z-score <-2.5	Pathological fracture	Pathological fracture causing life threatening consequences
Myalgia	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure

APPENDIX 4: Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Osteonecrosis	NA	Asymptomatic but with radiologic findings and no surgical intervention indicated	symptomatic with radiologic findings or surgical intervention indicated	Disabling bone pain with radiologic findings causing inability to care for self
Acute systemic allergic reaction	Localized urticaria with no medical intervention indicated	Localized urticaria with mild angioedema with no medical intervention indicated	Gen urticaria or angioedema with medical intervention indicated or bronchospasm	Anaphylaxis, laryngeal angioedema, laryngeal edema or life-threatening bronchospasm
Chills	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	NA
Fatigue/malaise	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Incapacitating symptoms, unable to perform basic self-care
Fever	99.8-101.5	101.6-102.8	102.9-104.9	>104.9
Pain	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Incapacitating symptoms, unable to perform basic self-care
Unintentional weight loss	NA	5-9% loss of body weight	10-19% loss of body weight	>19% loss of body weight or aggressive intervention indicated (feeding tube, TPN)
Lipodystrophy or lipoatrophy	detectable by subject	Detectable by provider	Obvious or disfiguring	NA
Diabetes mellitus (new onset)	NA	without indication for medications	Medications indicated	Life threatening consequences
Diabetes mellitus (existing)	NA	Requiring modification of medications	Lack of control despite medication modification	Life threatening consequences
Gynecomastia	detectable by subject	Detectable by provider	Obvious or disfiguring	NA
Hyperthyroidism	asymptomatic	Symptoms causing moderate impact of activities OR medication indicated	Symptoms causing inability to perform activities OR medication indicated	Life threatening consequences
Hypothyroidism	asymptomatic	Symptoms causing moderate impact of activities OR medication indicated	Symptoms causing inability to perform activities OR uncontrolled despite medication	Life threatening consequences
Intermenstrual bleeding	Spotting	≤ typical menstrual cycle	≥ typical menstrual cycle	Hemorrhage with life threatening hypotension

APPENDIX 4: Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Urinary obstruction (i.e. stone)	NA	Without hydronephrosis or acute kidney injury	With hydronephrosis or acute kidney injury	Life threatening consequences
Infection (other than HIV)	Localized, no systemic antimicrobial treatment indicated AND symptoms causing minimal impact on activities	Systemic antimicrobial treatment indicated OR symptoms causing >minimal impact on activities	Systemic antimicrobial treatment indicated AND symptoms inability to perform activities OR operation intervention indicated (beyond simple I&D)	Life threatening consequences (i.e. septic shock)

APPENDIX 5: Study Procedure Schedule

	Screening/Baseline combined visit	Screening (if not same day as screen)	Baseline (if not same day as screen)	1 Month	4 Month	Early Discontinuation
Vitals	**X**	**X**	**X**	**X**	**X**	**X**
MAAS	**X**	**X**		**X**	**X**	**X**
HIV-SI	**X**		**X**	**X**	**X**	**X**
History and Physical	**X**	**X**				
History and Symptom based physical			**X**	**X**	**X**	**X**
Complete Blood Count	**X**		**X**	**X**	**X**	**X**
CD4 panel	**X**		**X**	**X**	**X**	**X**
Complete Metabolic Panel	**X**		**X**	**X**	**X**	**X**
HIV-1 Quantitative viral load	**X**		**X**	**X**	**X**	**X**
Urinalysis	**X**		**X**	**X**	**X**	**X**
HIV Genotype	if viral load >200 copies/mL at last check		if viral load >200 copies/mL at last check	if viral load >200 copies/mL at last check	if viral load >200 copies/mL at last check	if viral load >200 copies/mL at last check
Urine pregnancy	if indicated		if indicated	if indicated	if indicated	if indicated
Hepatitis B viral load	if indicated		if indicated	if indicated	if indicated	if indicated

APPENDIX 6: Contraindicated Concomitant Medications

Alpha 1-Adrenoreceptor Antagonist	alfuzosin
Antiarrhythmics/Antianginals	amiodarone, dronedarone, ivabradine, lidocaine (systemic)
Anti-coagulants	apixaban,rivaroxaban, esclicabazepine
Anti-convulsants	carbamezepine, phenobarbital, phenytoin, oxcarbazepine
Anti-gout	colchicine (in patients with renal and/or hepatic impairment)
Antimycobacterial	Rifampin, rifapentine, rifabutin
Ergot Derivatives	Such as: dihydroergotamine, ergonovine, ergotamine
Hepatitis C Virus Direct-Acting Antivirals	elbasvir/grazoprevir , glecaprevir/pibrentasvir, simeprevir
Herbal Products St.	John's wort (Hypericum perforatum)
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin
Other Lipid Modifying Agents	lomitapide
Inhaled Beta Agonist	salmeterol
Neuroleptics	lurasidone, pimozide
Opioid Antagonist	naloxegol
PDE-5 Inhibitor	sildenafil (for treatment of pulmonary arterial hypertension), avanafil
Platelet Aggregation Inhibitor	ticagrelor
Sedatives/Hypnotics	triazolam
Antiplatelet	ticagrelor
antineoplastic	Everoliumus, irinotecan
antifungals	voriconazole
Steroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone

APPENDIX 7: Positive Screen Criteria for Part 2

Positive screen for Part II one positive response in both columns:	
One from below	One from below
Question 3 = “Yes”	Question 8 = not “always” or “almost always”
Question 7 = “Yes”	Question 9 = greater than 2
Question 11 = “Side effect(s)” or named side effect	Question 10 = greater than 2