Clinical Trial Protocol

AIC316-03-I-07

A double-blind, single-center, randomized, placebo- and positive-controlled, parallel-group trial with a nested crossover part on the electrocardiographic effects of 100 and 400 mg pritelivir per day in healthy subjects: a thorough QT/QTc trial

Product/formulation	Pritelivir 100 mg tablets
Phase	Phase 1
Indication	Not applicable
EudraCT number	2022-000203-12
Sponsor	AiCuris Anti-infective Cures AG Friedrich-Ebert-Strasse 475 42117 Wuppertal, Germany
Principal Investigator	Dr Jorg Taubel, MD, FFPM, FESC Richmond Pharmacology Ltd.
Trial Center	Richmond Pharmacology Ltd. 1a Newcomen Street, London Bridge, London SE1 1YR, United Kingdom
Responsible Medical Director	Dirk Kropeit, MD, PhD AiCuris Anti-infective Cures AG [redacted]
Version	V2.0
Date	25Nov2022

Confidentiality Statement

The information contained herein is confidential and the sole property of AiCuris. Any unauthorized use or disclosure of such information without the prior written authorization of AiCuris is strictly prohibited.

APPROVAL SIGNATURE PAGE

I have read and agree with this protocol and will follow the described procedures.

I agree to conduct the trial according to the protocol in compliance with the current accepted Declaration of Helsinki and the ICH-GCP guidelines. The Investigator(s) agree(s) to provide direct access to source data and trial-related documents for trial-related monitoring and auditing by the Sponsor and inspection by the appropriate regulatory authorities.

Dr Jorg Taubel, MD, FFPM, FESC
Principal Investigator
Richmond Pharmacology Ltd.

Date, Signature

Dirk Kropeit, MD, PhD
AiCuris Responsible Physician
AiCuris Anti-infective Cures AG

Date, Signature

[redacted]
Responsible Biostatistician
Richmond Pharmacology Ltd.

Date, Signature

[redacted]
Pharmacovigilance Manager
AiCuris Anti-infective Cures AG

Date, Signature

[redacted]
Responsible Pharmacokinetics Manager
Laboratory Head of Pharmacokinetics and Pharmacometrics
AiCuris Anti-infective Cures AG

Date, Signature

INVOLVED PARTIES

Investigators

This will be a single-center trial. The Principal Investigator will be:

Dr Jorg Taubel, MD, FFPM
Chief Executive Officer

Richmond Pharmacology Ltd.

1a Newcomen Street,
London Bridge,
London, SE1 1YR,
United Kingdom

[redacted]

Sponsor

Position	Name, Title
AiCuris Responsible Physician	Dirk Kropeit, MD, PhD Head of Early Clinical Development AiCuris Anti-infective Cures AG
Pharmacokinetics Manager	[redacted] Laboratory Head of Pharmacokinetics and Pharmacometrics AiCuris Anti-infective Cures AG
Pharmacovigilance Manager	[redacted] Pharmacovigilance Manager AiCuris Anti-infective Cures AG
Clinical Trial Manager	[redacted] Clinical Trial Manager AiCuris Anti-infective Cures AG
Bioanalytics Coordinator	[redacted] Bioanalytical Coordinator AiCuris Anti-infective Cures AG
Medical Writing	[redacted] External Medical Writing Consultant for AiCuris Anti-infective Cures AG

Contract Research Organization(s)

Position	Name, Title
Co-Investigator	[redacted]M Medical Director Richmond Pharmacology Ltd. 1a Newcomen Street London Bridge London, SE1 1YR United Kingdom
Monitoring Project Coordination	AMS Advanced Medical Services Ltd. 26-28 Hammersmith Grove London W6 BA United Kingdom
Project Management at clinical trial site	[redacted] Director of Study Management Richmond Pharmacology Ltd. 1a Newcomen Street London Bridge London, SE1 1YR United Kingdom
Research Physician	[redacted] Lead Speciality Research Physician Richmond Pharmacology Ltd. 1a Newcomen Street London Bridge London, SE1 1YR United Kingdom
Responsible Biostatistician	[redacted] Senior Biostatistician Richmond Pharmacology Ltd. 1a Newcomen Street London Bridge London, SE1 1YR United Kingdom
Consultant Statistician for ECG analyses	[redacted] Statistik Georg Ferber GmbH, Riehen, Switzerland
Data Management	[redacted] Head of Data Management Richmond Pharmacology Ltd. 1a Newcomen Street London Bridge London, SE1 1YR United Kingdom

Position	Name, Title
Pharmacokinetic evaluation	Venn Life Sciences ED Lage Mosten 29 NL-4822 NK Breda The Netherlands
Safety laboratory	The Doctors Laboratory The Halo Building 1 Mabledon Place London, WC1H 9AX United Kingdom
SARS-CoV-2 polymerase chain reaction testing	Richmond Pharmacology Ltd. 1a Newcomen Street London Bridge London, SE1 1YR United Kingdom
Bioanalytics	A&M Labor für Analytik und Metabolismusforschung Service GmbH Kopernikusstraße 25 50126 Bergheim, Germany
Pharmacogenomics	IMGM Laboratories GmbH Lochhamer Str. 29a Martinsried, Germany
Pharmacovigilance (SAE reporting)	IQVIA Eastpoint Business Park, Fairview Dublin 3, Ireland

IN CASE OF EMERGENCY

For urgent medical advice the AiCuris Medical Expert on duty is available 24 h per day under the following:

24h emergency number

Number: [redacted]

For reporting of serious adverse events, please follow the procedures described in Section 6.6.4.1.8. The occurrence of SAEs will be notified by the Investigator to IQVIA immediately, without undue delay (at least within 24 hours) after becoming aware of their occurrence by completing the corresponding AE/SAE eCRF which generates an alert notification to IQVIA. If no transmission via eCRF/internet is possible, the completed SAE form must be sent to the following:

24 h SAE reporting

Free-Fax Number: [redacted]

Or

Email: [redacted]

1 SYNOPSIS

Name of Sponsor/Company:	AiCuris Anti-infective Cures AG
Title of the trial: A double-blind, single-center, randomized, placebo- and positive-controlled, parallel-group trial with a nested crossover part on the electrocardiographic effects of 100 and 400 mg pritelivir per day in healthy subjects: a thorough QT/QTc trial	
Principal Investigator: Dr. Jorg Taubel	
Study center(s): Richmond Pharmacology	
Planned trial period (years): Q4 2022 to Q2 2023	**Phase of development:** Phase 1

Objectives:

Primary objective

- to define the effects of pritelivir on the QTcF interval derived from 12-lead ECGs in comparison with placebo in male and female subjects

Secondary objectives

- to assess pharmacokinetic properties of multiple doses of pritelivir and to examine the correlations between pritelivir plasma concentration and its effects, if any, on the QTcF interval
- to evaluate additional electrocardiographic effects of pritelivir
- to show the trial's assay sensitivity by assessing the effects of moxifloxacin (positive control vs. placebo) on the QTcF interval
- to investigate the safety and tolerability of pritelivir

Trial design

Subjects will be in-house from Day -2 to Day 20 and will be randomized to one of the 2 parallel treatment groups (as part of the blind, both groups will receive the same number of tablets and capsules at the same timepoints, though some will be verum and some will be placebo depending on the randomized regimen). Group 1 will receive a therapeutic and a supra-therapeutic dose of pritelivir plus moxifloxacin placebo. Group 2 will receive pritelivir placebo as well as moxifloxacin and matching placebo (nested crossover: Group 2a and Group 2b). 12-lead ECG triplicates will be recorded from the bedside 12-lead ECG on the Days -1, 1, 2, 6, 16, and 17 and will be analyzed afterwards in each group for these 6 days of documentation by a blinded reader.

It is of note that Holter ECG data will be collected in parallel at Screening to exclude anyone with pre-existing cardiac abnormalities as well as on Days -1, 1, 2, 6, 16, and 17 as a back-up for the bedside 12-lead ECGs.

In Group 1, 32 male and female subjects (at least 12 subjects per sex) will receive a loading dose of 400 mg pritelivir on Day 1. Afterwards they will receive 100 mg pritelivir qd from Day 2 to 6 and 400 mg pritelivir qd from Day 7 to 16. Furthermore, these subjects will receive matching moxifloxacin placebo on the Days 2 and 17.

In Group 2, 32 male and female subjects (at least 12 subjects per sex) will receive the respective amounts of tablets of matching pritelivir placebo from Day 1 to Day 16 in Group 2 as verum tablets in Group 1. Furthermore, subjects in Group 2a (16 male and female subjects) will receive 400 mg moxifloxacin on Day 2 and matching moxifloxacin placebo on Day 17 and subjects in Group 2b (16

male and female subjects) will receive 400 mg moxifloxacin on Day 17 and matching moxifloxacin placebo on Day 2.

To maintain double-blinding the following measures will be needed, and data evaluations generated for Group 1 and Group 2:

- 12-lead ten second ECG triplicates will be digitally recorded and analyzed (from the bedside 12-lead-ECG devices) in subjects of both groups on the Days -1, 1, 2, 6, 16 and 17.
- PK samples will be collected from subjects of both groups on the Days 1, 6, and 16 for pritelivir and the metabolites AIC090015 and AIC090105 as well as for moxifloxacin on the Days 2 and 17.
- Over-encapsulated moxifloxacin- and matching placebo will be used.

Number of subjects (planned):

64 (32 subjects per group; at least 12 of each sex in each group)

Diagnosis and main criteria for inclusion:

Adult healthy male and female subjects of any ethnic origin (18 to 45 years inclusive).

Test product, dose, and mode of administration:

- Pritelivir 100 mg tablet, oral administration

Duration of treatment:

Subjects will be in-house from Day -2 to Day 20.

Reference therapy, dose, and mode of administration

- Pritelivir placebo tablets
- Moxifloxacin 400 mg capsule, oral administration
- Matching moxifloxacin placebo capsule, oral administration

Criteria for evaluation:

Efficacy

Not applicable

ECG variables

The following parameters will be analyzed after being derived from the bedside 12-lead ECG measurements (10-second triplicate recordings):

Primary variable (related to the primary endpoint)

- QTc using Fridericia correction method (QTcF)

Secondary variables

- Heart rate
- PR interval
- QRS interval
- Uncorrected QT interval
- Change in ECG morphological patterns

Pharmacokinetics

The following parameters of pritelivir and its metabolites AIC090015 and AIC090105 will be determined:

- C_{0h} (trough levels) of pritelivir, AIC090015 and AIC090105 on the Days 1 to 5 and 13 to 15,
- AUC_{τ}, C_{max}, t_{max}, t_{lag}, CL/F, V_d/F, MRT of pritelivir in plasma on Day 1,
- $AUC_{\tau,ss}$, $C_{ss,max}$, C_{min}, $C_{ss,av}$, t_{max}, CL_{ss}/F, $V_{d,ss}$/F, MRT of pritelivir in plasma on Days 6 and 16,
- AUC_{τ}, C_{max}, t_{max}, t_{lag}, MRT of metabolites AIC090015 and AIC090105 in plasma on Day 1.

- $AUC_{\tau,ss}$, $C_{max,ss}$, C_{min}, $C_{ss,av}$, t_{max}, MRT of metabolites AIC090015 and AIC090105 in plasma on Days 6 and 16.

Moxifloxacin plasma concentrations will be measured using a validated assay for the purpose of the concentration-effect analysis to demonstrate assay sensitivity. Only concentrations will be reported, but no pharmacokinetic analysis will be reported.

Pharmacogenomics/gene expression

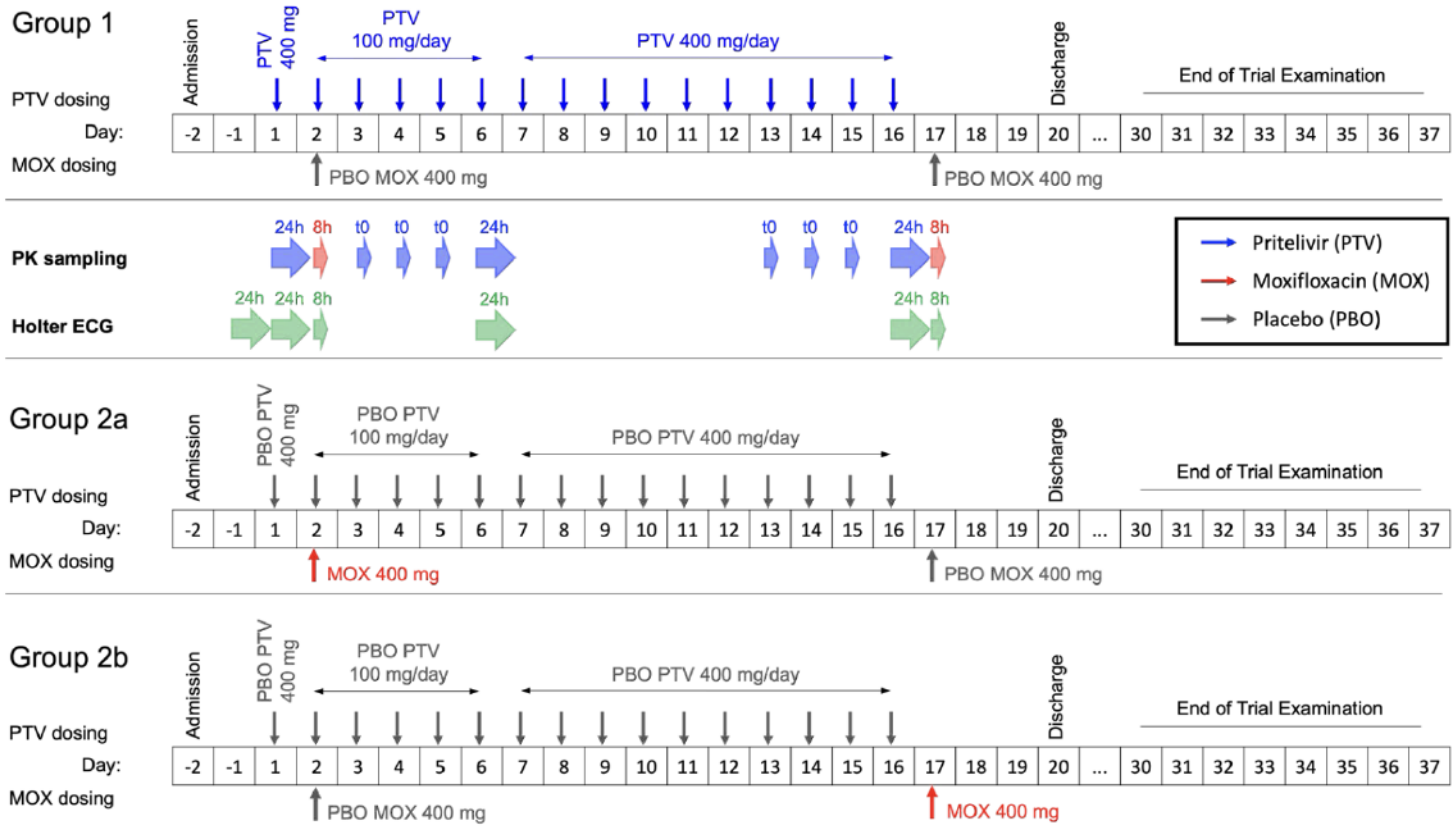
Post-hoc analysis of alleles associated with altered drug metabolism/ disposition may be performed.

Safety and tolerability

- Overall tolerability
- Nature, frequency, duration, intensity, seriousness, and causality of adverse events
- Physical examination, vital signs, and body temperature
- Clinical laboratory parameters: serum chemistry, hematology and coagulation parameters, urinalysis
- Standard 12-lead ECG collected using a 12-lead ECG device

Date of protocol: 25Nov2022

SCHEMATIC OVERVIEW OF THE TRIAL DESIGN



SCHEDULE OF TRIAL PROCEDURES

Period	Screening			Treatment Period									EoT
Day	-21 to -3	-2	-1	1	2	3 to 5	6	7 to 15	16	17	18 to 19	20	30 to 37
Admission to Phase 1 unit		X											
Informed consent	X												
Inclusion/exclusion criteria	X	X	X										
Medical history	X												
Height and weight	X												
Demographics	X												
Check on lifestyle and habits	X												
Urine test for drug abuse	X	X											
Alcohol breath test	X	X											
Physical examination	X	X											X
Body temperature	X	X											X
Serology [1)]	X												
SARS-COV-2 monitoring	X [2)]												
Serum β-HCG [3)]	X												X
Urine β-HCG [3)]		X											
FSH test [4)]	X												

Period	Screening			Treatment Period									EoT
Day	-21 to -3	-2	-1	1	2	3 to 5	6	7 to 15	16	17	18 to 19	20	30 to 37
Vital signs [5) 6)]	X	X	X				X [5)]		X [5)]			X	X
12-lead ECG [5) 7)]	X	X	X	X [5)]	X		X [5)]		X [5)]	X		X	X
Holter-ECG	X		X	X	X		X		X	X			
Safety laboratory [5), 8)]	X	X					X [5)]		X [5)]			X	X
Pharmacogenomics sample				X [9)]									
Dosing: Pritelivir 400 mg (Group 1) OR Matching placebo (Group 2)				X				X	X				
Dosing: Pritelivir 100 mg (Group 1) OR Matching placebo (Group 2)					X	X	X						
Dosing: Moxifloxacin (Group 2 only) OR Matching placebo (Groups 1 and 2)					X					X			

Period	Screening			Treatment Period									EoT
Day	**-21 to -3**	**-2**	**-1**	**1**	**2**	**3 to 5**	**6**	**7 to 15**	**16**	**17**	**18 to 19**	**20**	**30 to 37**
PK blood samples for plasma pritelivir and metabolites PK [5)]				X [5)]	Trough sample D2	Trough samples D3-5	X [5)]	Trough samples D13-15	X [5)]	Trough sample D17			
PK blood samples for moxifloxacin determination [5)]					X [5)]					X [5)]			
Adverse events questioning [10)]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication [11)]	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from Phase 1 unit												X	

β-HCG=beta-human chorionic gonadotropin; ECG=electrocardiogram; EoT=End of Trial; FSH=follical stimulating hormone; PK=pharmacokinetics; SARS-COV-2=severe acute respiratory syndrome coronavirus 2

1) HIV-I- and HIV-II-antibodies, HBsAg, anti-HBc (IgG + IgM), and anti-HCV
2) COVID-19 tests will be carried out at regular intervals, prior to entry in the unit and throughout the residential period as per the latest Richmond Pharmacology COVID-19 Infection Control Guidelines and pre-entry algorithms.
3) Women only
4) Women of non-childbearing potential who have a history of no menses of at least 24 months
5) Detailed timings of individual PK samples, safety lab samples, vital sign measurements and supine times, ECGs, and meals are given in table Timing of repeat measure samples.
6) Vital signs include blood pressure and pulse rate that will be measured after a supine time of at least 5 minutes.
7) 12-lead ECG will be measured in triplicate after a rest period of at least 10 minutes.
8) Serum chemistry, hematology and coagulation parameters, urinalysis
9) Pre-dose

10) Skin reaction checks included
11) On dosing days, the concomitant medication should always be checked pre-dose

TIMING OF REPEAT MEASURE SAMPLES

Study Day	Time (h)	PK sampling 1 [a)] (plasma)	PK sampling 2 [b)] (plasma)	Meals [c)]	Vital Signs [d)]	ECG [e)]	Hematology/ Biochemistry/ Coagulation
Day -1	-1					X	
	-40 mins					X	
	-20 mins					X	
	0				X		
	15 mins					X	
	30 mins					X	
	45 mins					X	
	1					X	
	1.5						
	2				X	X	
	3					X	
	4			X [c)]	X	X	
	5					X	
	6					X	
	7					X	
	8			X		X [f)]	

Study Day	Time (h)	PK sampling 1 [a)] (plasma)	PK sampling 2 [b)] (plasma)	Meals [c)]	Vital Signs [d)]	ECG [e)]	Hematology/ Biochemistry/ Coagulation
	10						
	11						
	12			X	X	X	
Day 1	-1					X	
	-40 mins					X	
	-20 mins					X	
	Pre-dose (0 h)	X					
	15 mins	X				X	
	30 mins	X				X	
	45 mins	X				X	
	1	X				X	
	1.5	X					
	2	X				X	
	3	X				X	
	4	X		X [c)]		X	
	5	X				X	
	6	X				X	

Study Day	Time (h)	PK sampling 1 [a)] (plasma)	PK sampling 2 [b)] (plasma)	Meals [c)]	Vital Signs [d)]	ECG [e)]	Hematology/ Biochemistry/ Coagulation
	7	X				X	
	8	X		X		X [f)]	
	10	X					
	11						
	12	X		X		X	
Day 2	-1					X	
	-40 mins					X	
	-20 mins					X	
	Pre-dose (0 h)	X	X				
	1		X			X	
	2		X			X	
	3		X			X	
	4		X	X [c)]		X	
	5		X			X	
	6		X			X	
	7		X			X	
	8		X	X		X [f)]	

Study Day	Time (h)	PK sampling 1 [a)] (plasma)	PK sampling 2 [b)] (plasma)	Meals [c)]	Vital Signs [d)]	ECG [e)]	Hematology/ Biochemistry/ Coagulation
	12			X			
Day 3	Pre-dose (0 h)	X					
	1			X			
Day 4	Pre-dose (0 h)	X					
	1			X			
Day 5	Pre-dose (0 h)	X					
	1			X			
Day 6	-1					X	
	-40 mins					X	
	-20 mins					X	
	Pre-dose (0 h)	X			X		X
	15 mins	X					
	30 mins	X					
	45 mins	X					
	1	X				X	
	1.5	X					
	2	X			X	X	

Study Day	Time (h)	PK sampling 1 [a)] (plasma)	PK sampling 2 [b)] (plasma)	Meals [c)]	Vital Signs [d)]	ECG [e)]	Hematology/ Biochemistry/ Coagulation
	3	X				X	
	4	X		X [c)]	X	X	
	5	X				X	
	6	X				X	
	7	X				X	
	8	X		X		X [f)]	
	10	X					
	11						
	12	X		X	X	X	
Day 7	24	X				X	
Day 13	Pre-dose (0 h)	X					
	1			X			
Day 14	Pre-dose (0 h)	X					
	1			X			
Day 15	Pre-dose (0 h)	X					
	1			X			
Day 16	-1					X	

Study Day	Time (h)	PK sampling 1 [a)] (plasma)	PK sampling 2 [b)] (plasma)	Meals [c)]	Vital Signs [d)]	ECG [e)]	Hematology/ Biochemistry/ Coagulation
	-40 mins					X	
	-20 mins					X	
	Pre-dose (0 h)	X			X		X
	15 mins	X					
	30 mins	X					
	45 mins	X					
	1	X				X	
	1.5	X					
	2	X			X	X	
	3	X				X	
	4	X		X [c)]	X	X	
	5	X				X	
	6	X				X	
	7	X				X	
	8	X		X		X [f)]	
	10	X					
	11						

Study Day	Time (h)	PK sampling 1 [a)] (plasma)	PK sampling 2 [b)] (plasma)	Meals [c)]	Vital Signs [d)]	ECG [e)]	Hematology/ Biochemistry/ Coagulation
	12	X		X	X	X	
Day 17	-1					X	
	-40 mins					X	
	-20 mins					X	
	Pre-dose (0 h)	X	X				
	1		X			X	
	2		X			X	
	3		X			X	
	4		X	X [c)]		X	
	5		X			X	
	6		X			X	
	7		X			X	
	8		X	X		X [f)]	
	11						
	12			X			
	24						

Study Day	Time (h)	PK sampling 1 [a] (plasma)	PK sampling 2 [b] (plasma)	Meals [c]	Vital Signs [d]	ECG [e]	Hematology/ Biochemistry/ Coagulation
Day 20	Morning				X	X	X

a) PK sample 1: pritelivir and metabolites in plasma.
b) PK sample 2: moxifloxacin in plasma.
c) On D-1 and dosing days, the first meal will be lunch given at H 4 post dose. Afternoon snack will be given at H 7 and dinner at H 11.
d) Vital signs include blood pressure, pulse rate, will be measured after a supine time of at least 5 min.
e) 12-lead ECG will be measured in triplicate after a rest period of at least 10 min.
f) Light exercise to be undertaken after H 8 ECG (Further details to be included in Study Operations Manual [SOM])

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	adverse event
AIDS	acquired immune deficiency syndrome
AUC	area under the analyte concentration-time curve
β-HCG	beta human chorionic gonadotropin
BMI	body mass index
CA	Competent Authority
C_{av}	average plasma concentration
CK	creatine kinase
CL/F	total apparent clearance
C_{max}	maximum observed analyte plasma concentration
C_{min}	minimum observed analyte plasma concentration
COVID-19	coronavirus disease 2019
CRO	Contract Research Organization
CYP	cytochrome P isoenzyme
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DDI	drug-drug interactions
DHP	Data Handling Protocol
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EoT	End of Trial
FDA	(United States) Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus

Abbreviation	Explanation
HR	heart rate
HSV	herpes simplex virus
IC_{50}	concentration at half-maximal inhibition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig(M/G)	immunoglobulin (class M/class G)
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
MTS	Master Treatment Schedule
NHS	(UK) National Health Service
PGx	pharmacogenomics
PI	Principal Investigator
PK	pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamics
PKS	pharmacokinetic set
qd	once daily
QP	Qualified Person
QTcF	corrected QT interval using Fridericia's formula
RA	Regulatory Authority
RP	Research Physician
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	System Organ Class
SOM	Study Operations Manual
SPC	Summary of Product Characteristics
ss	steady state
STW	Scheduling Time Windows
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
t_{lag}	time period between the time of dosing and the time of the first observation with a measurable non-zero concentration

Abbreviation	Explanation
t_{max}	time to maximum observed plasma concentration
TQT	thorough QT (trial)
UK	United Kingdom
V_d/F	apparent volume of distribution
WHO-DRUG	World Health Organisation Drug Dictionary

LIST OF TABLES

LIST OF FIGURES

Not applicable.

2 INTRODUCTION

2.1 Background information

Pritelivir

Pritelivir is a novel anti-herpes simplex virus (HSV) inhibitor and belongs to the helicase-primase inhibitors, which have a mode of action that is distinct to that of antiviral nucleoside analogs currently in clinical use. Pritelivir is active against both HSV types, HSV-1 and HSV-2, and prevents de novo synthesis of virus deoxyribonucleic acid (DNA) through inhibition of the viral helicase-primase complex whereas the nucleoside analogs terminate ongoing DNA chain elongation through inhibition of viral DNA polymerase. Pritelivir does not require activation by viral thymidine kinase. Pritelivir is active against nucleoside-analog resistant virus strains.

Nonclinical safety pharmacology studies in Beagle dogs showed no adverse cardiac effects: there was no indication of effects upon systolic, diastolic and mean peripheral arterial blood pressure, heart rate, cardiac output, stroke volume, systolic left ventricular pressure, maximum dp/dt, central venous pressure as well as respiratory rate and volume, blood pH, and blood gases. No evidence was noted for a prolongation of the QT interval.

In vitro studies using whole-cell patch-clamp technique was used to investigate the effects of pritelivir on hERG potassium channels in stably transfected HEK293 cells (human embryonic kidney cells) revealed a concentration-dependent inhibition of hERG-mediated tail current amplitude (IC_{50} ~ 156 µM). The inhibitory effect of pritelivir was significant at 10 µM (remaining current 82 ±10%) but still far away from being complete at the solubility limit of about 50 µM (remaining current 75 ±9%) and at least partially reversible upon wash-out. However, since the IC_{50} (hERG) is more than 100-fold greater than the mean therapeutic C_{max} values when corrected for free fraction (from 109-fold for the 400 mg/day to 355-fold for the 100 mg/day dose group at steady state), the interaction between pritelivir and hERG is of negligible clinical relevance in humans.

Moxifloxacin

Moxifloxacin is normally used to treat a variety of bacterial infections and belongs to the class of quinolone antibiotics. The role of moxifloxacin in this trial is to demonstrate the trial's ability to detect a small effect on the QT interval (assay sensitivity), since moxifloxacin is known to have a mild QT prolonging effect that has been used in the majority of thorough QT/QTc trials [1, 2]. Further information on moxifloxacin can be obtained from the current SPC.

2.2 Rationale for the trial

As recommended by the International Conference for Harmonisation (ICH) E14 Guidance for Industry [3, 4] the present thorough QT/QTc trial is designed to investigate the potential of pritelivir to cause QT/QTc prolongation.

2.3 Risk/benefit assessment

The current risk/benefit assessment for a therapeutic dose of 100 mg/day pritelivir is given in Section 6 "Guidance for the Investigator" of the Investigator's Brochure. As in the current trial a supratherapeutic dose of 400 mg/day dose of pritelivir is administered, a specific Risk/Benefit is discussed below in this section.

The selected doses of pritelivir planned for this trial are classified to be high enough for the investigation of a possible influence of pritelivir on the QT/QTc interval. The choice of doses is explained in Section 6.2.2.

No effect on any ECG parameter, including QT and QTcF, could be detected in clinical trials by classical 12-lead safety ECGs so far for doses up to 400 mg pritelivir per day. Furthermore, pritelivir has not shown any relevant effect on ECGs in Beagle dogs (safety pharmacology) or on the hERG channel.

A by-species summary of multiples-of-exposure (MoEs) for NOAELs vs the human steady-state at 400 mg/day dose is given in Table 2-1. The MoEs for total AUC and C_{max} are close to 1 or above for all species; the MoEs are below 1 for unbound AUC and C_{max} especially in rats, dogs, and monkeys.

Table 2-1 By-species multiples-of-exposure for NOAELs vs human steady state at 400 mg/day dose

Species	Duration of exposure	NOAEL (mg/kg/day)	C_{max} at NOAEL (µg/mL)	MoE [a] for C_{max} (total/free)	AUC at NOAEL (µg·h/mL)	MoE [a] for AUC (total/free)	Gender (TK)
Mouse	13 weeks	100	101	5/1.8	1,380	4/1.5	m
			114	6/2.0	1,580	5/1.7	f
			108	5/1.9	1,480	4/1.6	m+f
Rat	26 weeks	10	24.2	1.2/0.5	234	0.7/0.3	m
			35.4	1.7/0.8	329	1.0/0.4	f
			29.8	1.5/0.6	282	0.8/0.4	m+f
Rat Seg I	13 weeks	50	54.9	2.7/1.2	681	2.0/0.9	m
Dog	13 weeks	30 [b]	39.1	1.9/0.7	628	1.9/0.7	m
			49.7	2.4/0.9	683	2.0/0.8	f
			44.4	2.2/0.8	655	1.9/0.7	m+f
Monkey	39 weeks	25	42.0	2.0/0.6	766	2.3/0.6	m
			26.8	1.3/0.4	461	1.4/0.4	f
			34.4	1.7/0.5	614	1.8/0.5	m+f

AUC=area under the plasma concentration time curve; C_{max}=maximum observed plasma concentration; LOAEL=lowest observed adverse effects level; MoE=multiple of exposure; NOAEL=no observed adverse effect level; TK=toxicokinetic

Note: Urinary hyperplasia is a known rodent-specific effect and it has only been observed in rodents. Therefore, urinary hyperplasia is not considered relevant for the calculation of safety margins, ie, MoEs

a) MoEs calculated vs observed human (male) exposure at 400 mg/day dose in trial AIC316-01-I-05

b) LOAEL was used since NOAEL was not identified

The adverse effects detected at the dose levels above the NOAEL in the respective species showed exposures leading to MoEs of 1 and above even for unbound AUC and C_{max}. Key findings above these dose levels were urinary hyperplasia, impaired male fertility, hematological changes, liver effects and cataracts in rodents, hematological changes in dogs, and hematological

and skin findings in monkeys; these are discussed further in Section 4.3.2 of the Investigator's Brochure. The findings occurred after a much longer treatment period than planned in the current clinical trial and they were, with one exception (skin findings; see below), not detected in a clinical trial in which 400 mg pritelivir was administered once daily up to 16 days.

The highest dose of 400 mg qd pritelivir (supratherapeutic dose) in the present thorough QT/QTc trial has already been investigated in male subjects in trial AIC316-01-I-05. In this trial, volunteers were treated with 200 mg once daily (21 days) or 400 mg once daily (up to 16 days); pritelivir was well tolerated in the 200 mg dosing group and also well tolerated up to Day 10 in the 400 mg dosing group, however, the trial was stopped prematurely due to the occurrence of AEs belonging to the SOC skin and subcutaneous tissue disorders; these were only observed in the 400 mg dose group; 5 of 16 subjects (4 of 12 subjects (33.3%) exposed to pritelivir, 1 of 4 subjects (25.0%) exposed to placebo) developed a macular or maculo-papular skin reaction (exanthema or eruption), mainly between Day 11 to 14 of treatment. These mild skin reactions were not accompanied by formation of bullae, pustules or alterations of liver function tests or eosinophilia. A viral infection could have been the cause but also an effect of pritelivir could not be completely ruled out.

It is of note that only male subjects participated in the above-mentioned trial AIC316-01-I-05, but in the TQT trial, female subjects will also be included. However, based on data from the first-in-human trial AIC316-01-I-01, the DDI trial AIC316-03-I-01 as well as Phase 2 trials, similar exposures can be expected in men and women in this TQT trial.

The risk mitigation measures for potential risks are given in Appendix 3.

This trial will be conducted in a specialized early phase Clinical Pharmacology Unit with onsite resuscitation equipment and medication, in addition to access to an acute hospital with Critical Care facilities, thus ensuring direct access to equipment and staff for resuscitating and stabilizing subjects in acute medical conditions and emergencies. The trial is conducted by a PI and well trained medical and technical staff with ample experience in the conduct of early phase clinical trials. The trial is designed to closely monitor, treat and communicate potential expected adverse reactions as well as potential unexpected adverse events.

The individual subjects in this clinical trial will not benefit from the treatment. Inclusion and exclusion criteria have been chosen to enable a uniform trial sample of subjects and to minimize possible risks due to administration of pritelivir. The trial is designed to closely monitor, treat and communicate potential expected adverse reactions as well as potential unexpected adverse events. To ensure the safety of the subjects, adverse events, vital signs, physical examinations, electrocardiographic variables, and laboratory parameters will be monitored. Subjects will remain under medical supervision on the ward during the whole pritelivir/placebo treatment period until 4 days after last treatment.

In the unlikely case that adverse events from SOC skin and subcutaneous tissue disorders occur to such an extent or severity that subjects have to be withdrawn from the trial, the supratherapeutic dose may be reduced to 200 mg/day pritelivir i) in an individual subject for the rest of the dosing phase, or ii) it may even be decided to suspend further dosing of all subjects (see Appendix 2). A general reduction of the therapeutic dose to 200 mg/day for all following subjects will be decided by the Sponsor and the Principal Investigator and requires regulatory approval via a substantial amendment by RA and EC.

In summary, potential risks were identified during the nonclinical development of pritelivir. None of these potential risks have been observed in clinical trials with supratherapeutic doses up to 200 mg/day for 21 days or, with the exception of skin findings, up to 400 mg/day for up to 16 days. It remains unknown whether the skin and subcutaneous tissue disorder events were caused by pritelivir, however, if such events would occur, risk mitigation would be performed as described above.

In conclusion, the expected highest pritelivir exposure in this TQT trial after 400 mg qd pritelivir dosing at steady state is already covered by previous clinical trial- and nonclinical data.

3 TRIAL OBJECTIVES

Primary objective

- to define the effects of pritelivir on the QTc interval derived from 12-lead ECGs in comparison with placebo in male and female subjects.

Secondary objectives

- to assess pharmacokinetic properties of multiple doses of pritelivir and to examine the correlations between pritelivir plasma concentration and its effects, if any, on the QTcF interval,
- to evaluate additional electrocardiographic effects of pritelivir,
- to show the trial's assay sensitivity by assessing the effects of moxifloxacin (positive control vs. placebo) on the QTcF interval,
- to investigate the safety and tolerability of pritelivir.

4 TRIAL DESIGN

4.1 Overall trial design

This Phase 1 clinical trial is a double-blind, single-center, randomized, placebo- and positive-controlled, parallel-group, 'nested crossover' trial with multiple oral dose administration of pritelivir or matching placebo as well as a single oral administration of moxifloxacin (positive control) and corresponding matching placebo in healthy male and female subjects.

Subjects will be in-house from Day -2 to Day 20 and will be randomized to one of the 2 parallel treatment groups: Group 1 will receive a therapeutic and a supra-therapeutic dose of pritelivir plus moxifloxacin placebo. Group 2 will receive pritelivir placebo as well as moxifloxacin and matching placebo (nested crossover: Group 2a and Group 2b). 12-lead ECG triplicates will be recorded from the bedside 12-lead-ECG on the Days -1, 1, 2, 6, 16, and 17 and will be analyzed afterwards in each group for these 6 days of documentation by a blinded reader.

It is of note that Holter ECG data will be collected in parallel at screening to exclude anyone with pre-existing cardiac problems as well as on Days -1, 1, 2, 6, 16, and 17 as a back-up for the bedside 12-lead-ECGs.

In Group 1, 32 male and female subjects (at least 12 subjects per sex) will receive a loading dose of 400 mg pritelivir on Day 1. Afterwards they will receive 100 mg pritelivir qd from Day 2 to 6

and 400 mg pritelivir qd from Day 7 to 16. Furthermore, these subjects will receive matching moxifloxacin placebo on the Days 2 and 17.

In Group 2, 32 male and female subjects (at least 12 subjects per sex) will receive the respective amounts of tablets of matching pritelivir placebo from Day 1 to Day 16 in Group 2 as verum tablets in Group 1. Furthermore, subjects in Group 2a (16 male and female subjects) will receive 400 mg moxifloxacin on Day 2 and matching moxifloxacin placebo on Day 17 and subjects in Group 2b (16 male and female subjects) will receive 400 mg moxifloxacin on Day 17 and matching moxifloxacin placebo on Day 2.

Different measures will be needed, and data evaluations generated for Group 1 and Group 2, however, to maintain double blinding between Group 1 and Group 2;

- 12-lead ECG triplicates will be recorded and analyzed from the bedside 12-lead-ECG devices in subjects of both groups on the Days -1, 1, 2, 6, 16 and 17.
- PK samples will be collected from subjects of both groups on the Days 1, 6, and 16 for pritelivir and the metabolites AIC090015 and AIC090105 as well as for moxifloxacin on the Days 2 and 17.
- Over-encapsulated moxifloxacin- and matching placebo will be used.

If AEs interfere with adequate ECG recording, a Risk Benefit Committee (participants from AiCuris as well as the Principal Investigator) might decide to lower the (supra-therapeutic) dose in individual subjects.

Risk Benefit Committee

A Risk Benefit Committee (RBC) consisting of at least the Principal Investigator, AiCuris Responsible Physician, and the Pharmacovigilance Manager will meet to decide in cases where (non-emergency) unblinding or reductions in supratherapeutic dose levels may be necessary, or any other case where the Sponsor or PI consider this necessary.

4.2 Discussion of design and choice of control groups

According to the requirements of the ICH E14-Guidance on QT/QTc interval prolongation [3, 4] concerning the design of 'thorough QT/QTc studies' in healthy volunteers, adequate methods of trial control including double-blinded administration using matching placebos, randomization, and concurrent use of a positive control group are enforced to reduce bias produced by subjects' and Investigators' expectations. Therefore, the present trial is designed as a double-blind, single-center, randomized, placebo- and positive-controlled, parallel-group trial with a nested crossover part on electrocardiographic effects of 100 and 400 mg pritelivir per day in healthy male and female subjects. It will be analyzed to determine whether oral pritelivir has a potential risk of causing QT/QTc prolongation after a multiple-dose administration of pritelivir and a single dose administration of moxifloxacin (positive control) as well as the corresponding matching placebos.

The multiple-dose regimen was chosen to achieve an adequate exposure of pritelivir (Group 1) with a parallel-group comparison versus placebo (Group 2) due to a known long half-life of pritelivir. The positive control using moxifloxacin (Group 2) will serve for the demonstration of assay sensitivity and will account for sequence effects based on a 'nested', placebo-controlled,

crossover design within Group 2 (ie, 2a vs. 2b). Blinding will be maintained by the use of the respective matching placebos to the IMPs and the conduct of identical procedures in each treatment group.

The proposed trial design has been discussed with the FDA who provided some additional points for consideration. The FDA feedback is attached to the protocol in Appendix 5.

5 SELECTION OF TRIAL POPULATION

Adult healthy male and female subjects of any ethnic origin (18 to 45 years inclusive).

5.1 Inclusion criteria

Subjects meeting the following criteria will be considered for inclusion into the trial:

1. Subject has been informed both verbally and in writing about the objectives of the clinical trial, the methods, the anticipated benefits and potential risks and the discomfort to which they may be exposed and has given written consent to participation in the trial prior to trial start and any trial-related procedure.
2. Healthy male and female subjects of any ethnic origin, aged between 18 and 45 years (inclusive). Assessed as healthy based on a Screening examination including medical history, physical examination, blood pressure, pulse rate, ECG assessment, and clinical laboratory results.
3. Male subjects not planning to father or to donate sperms for in vitro fertilization during the trial and for at least 3 months after dosing of trial medication. Adequate contraception (see below) must be used during sexual intercourse with women of childbearing potential to make sure the fathering of a child will be ruled out during the trial and during the 3 months after dosing of trial medication.
   Women of childbearing potential have to perform adequate contraception. They should also not donate ova during the trial and for at least 3 months after dosing of trial medication.
   Adequate contraception is defined as a combination of a highly effective method of birth control and additional barrier contraception.
   Highly effective method of birth control is defined as follows: combined (estrogen and progesterone) oral contraceptives, combined hormonal vaginal rings, hormone implants, hormone injectables, or intrauterine device that need to be in place for a period of at least 2 months prior to Screening and continue for at least 3 months after dosing of trial medication.
   Additional barrier contraception (the following methods are allowed: condom of the male, diaphragm with spermicide, cervical cap with spermicide) must be used for the duration of the trial, defined as from the time of Screening to the End of Trial examination, and for at least 3 months after dosing of trial medication. A single barrier method alone or abstinence alone is not acceptable. Homosexual female subjects who refrain from heterosexual intercourse for at least 3 months prior to Screening may be included without a contraceptive method if they agree to further refrain from heterosexual intercourse until the End of Trial examination, and for at least 3 months after dosing of trial medication.
   Women of non-childbearing potential may be included if surgically sterile (documented complete hysterectomy, supracervical hysterectomy or bi-tubal ligations; partial hysterectomy is not sufficient) or if postmenopausal (who have a history of no menses of at least 24 months at screening and postmenopausal status confirmed by FSH test at screening).

4. In women, negative serum β-HCG (beta-human chorionic gonadotropin) test at Screening and negative urine β-HCG test on Day -2.
5. Subject agrees to pharmacogenomic blood sampling.
6. Subject must be willing and able to swallow up to 4 tablets (pritelivir or matching placebo) and 1 capsule (over-encapsulated moxifloxacin or matching placebo) at least twice during the trial.
7. Normal body weight as evidenced by a Body Mass Index (BMI) ≥18.0 and ≤25.0 kg/m^2, and a body weight ≥50.0 kg at Screening.
8. Subjects must have a negative test result for HIV-I- and -II-antibody, HBsAg, anti-HBc (IgG + IgM) and anti-HCV at Screening.
9. Subjects must have negative urine tests for drugs of abuse (benzodiazepines, opiates, amphetamines, methadone, cocaine, cannabinoids, barbiturates, cotinine) and negative breath alcohol tests at Screening and Admission for the in-house phase (Day -2).
10. Normal triplicate 12-lead ECG measured after 10 minutes in the supine position at screening and on admission on Day -2 showing regular sinus rhythm with a well-defined end of T.
11. Normal 24-hour 12-lead ECG at screening.

5.2 Exclusion criteria

A subject will not be eligible for inclusion if any of the following criteria applies:

1. History or current evidence of clinically relevant allergies or idiosyncrasy to drugs or food.
2. History of any moderate or severe allergy or any known allergy to any active or inactive ingredient(s) of moxifloxacin IMP, pritelivir IMP, or their respective matching placebos.
3. Any special dietary requirements that would prevent the consumption of standardized meals.
4. History or current evidence of any clinically relevant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematologic, endocrine, metabolic, neurological, psychiatric, or other disease suspected to influence pharmacokinetics or safety of the IMP.
5. History or any current evidence of a dermatological condition requiring treatment by a GP or specialist (with the exception of burns, fungal infections, and/or warts).
6. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the trial, or may bias the result of the trial or the subject's ability to participate in the trial.
7. History of malignancy.
8. Has vital signs consistently outside of normal range at screening or Day -1. Acceptable normal range is as follows:
    - supine HR 40 - 100 bpm (after at least five minutes of supine rest)
    - supine blood pressure (after at least five minutes of supine rest):
        - systolic blood pressure: 90 - 130 mmHg
        - diastolic blood pressure: 40 - 90 mmHg
9. The history or presence of any of the following cardiac conditions: known structural cardiac abnormalities; family history of long QT syndrome; cardiac syncope or recurrent, idiopathic syncope; exercise-related clinically significant cardiac events; known cardiovascular disease.
10. Consistent abnormal interval readings for PR, QRS and QTc intervals (PR <120ms or >210ms, QRS >120ms or QTcF >450ms for males and >470ms for females).

11. Transient fascicular blocks, undue ectopic burden, junctional rhythm and any other ECG findings which may in the opinion of the Investigator make a subject unsuitable for inclusion in this clinical trial.
12. Chronic or clinically relevant acute infections or febrile illness within 5 days prior to administration of the IMP.
13. Clinically relevant abnormalities in serum chemistry, haematology and coagulation parameters, urinalysis. Specifically:
    - Participants with transaminases (AST/ALT) above ULN or total bilirubin x1.5 ULN, at Screening.
    - Hemoglobin below LLN at Screening.
    - Platelet count below LLN at Screening.
    - White Blood Count above ULN at Screening.
    - Participants with urinalysis indicative of underlying infection/pathology at Screening.
14. Magnesium or potassium outside normal range in safety laboratory
15. Subject is lactating or breastfeeding.
16. Subject has received or is planning to receive a COVID-19 vaccination within 4 weeks before first dose administration, or within one week after trial completion.
    Subject must also comply with the latest COVID-19 safety measures/testing applicable at the site at that time, for entry into the unit and during in-house stays.
    Note: COVID-19 tests will be carried out at regular intervals, prior to entry in the unit and throughout the residential period as per the latest Richmond Pharmacology COVID-19 Infection Control Guidelines and pre-entry algorithms.
17. Use of any medication (incl. over-the-counter medication) within 2 weeks before dosing on Day 1 or within less than 10 times the elimination half-life of the respective drug, or anticipated concomitant medication during the treatment period. Exceptions may be the use of hormonal contraception and hormone replacement therapy as well as single intake of a drug if judged by the Investigators to have no clinical relevance and no relevance for the trial objectives. Eg, limited amounts of paracetamol are allowed to treat painful intercurrent adverse events (eg, headache, migraine).
18. Consumption of methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, “powerdrinks”) from 24 h before dosing on Day -1 until discharge.
19. Consumption of alcohol and tobacco products within 48 h prior to admission to the clinic until discharge.
20. Diseases or surgery of the gastrointestinal tract which may interfere with drug absorption (note: this is not applicable for minor abdominal surgery such as eg, appendectomy and herniotomy).
21. Treatment with an investigational drug within 90 days or 5 half-lives preceding the first dose of trial medication (or as determined by the local requirement, whichever is the longer).
22. Donation of blood or blood products (excluding plasma) within 90 days prior to trial medication administration.
23. Smoking of more than 10 cigarettes/cigars/pipes per day and/or inability to refrain from smoking during confinement.
24. History or clinical evidence of substance and/or alcohol abuse within the 2 years before screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females), using the following NHS alcohol tracker https://www.nhs.uk/oneyou/for-your-body/drink-less/know-your-alcohol-units/

25. Has any finding that, in the view of the Investigator, would compromise the subject's safety requirements or their ability to comply with all the trial requirements.
26. Not able to communicate meaningfully with the Investigator and site staff.
27. Lack of ability or willingness to give informed consent.
28. Participation in an earlier clinical trial with pritelivir.
29. Vulnerable subjects (eg, persons kept in detention)

5.3 End of trial

The end of the trial will be defined as the last subject last visit.

6 INVESTIGATIONAL PLAN AND PROCEDURES

6.1 Trial procedures

6.1.1 Screening

"Screening" is defined as assessments to be made within 3 weeks prior to first administration of the IMP to determine eligibility of a particular subject for entry into this trial.

Subject Informed Consent must be signed before Screening examinations start.

A capsule of similar size compared to over-encapsulated moxifloxacin will be shown to the subjects to evaluate their willingness and ability to swallow a relatively big capsule twice during the trial.

The Screening examination is described in the Schedule of trial procedures.

Subjects who are eligible for the trial based on the Screening examinations will return to the ward in the afternoon of Day -2 for admission.

Additional subjects will be screened as reserve subjects. Reserve subjects who are eligible for enrollment will also be admitted to the clinical facility to ensure enough eligible subjects are available to fill the respective cohort.

6.1.2 Treatment Phase

If eligibility for the trial is confirmed, subjects will continue the in-house stay until discharge on Day 20.

A summary of trial procedures to be performed during the Treatment Phase is provided in the Schedule of trial procedures.

Note: Dietary and other restrictions (beyond those given in the inclusion/exclusion criteria) are detailed in Section 6.2.5.

6.1.3 End of Trial examination (Day 30-37)

The End of Trial examination (EoT) will be performed 14 to 21 days after last dosing, on Day 30 up to Day 37.

Aim of the End of Trial examination is to guarantee the well-being of subjects and to verify that all values tested during the Pre-trial examination have remained within a clinically acceptable

range. Values that are out-of-range and clinically significant will be followed up until they return to the reference range or until there is an adequate explanation.

Any Aes will be followed up until the condition is resolved or there is an adequate explanation. If the subject refuses to follow the instructions of the Investigator, the latter is released from responsibility.

6.1.4 Early Termination

In case of an Early Termination, procedures will be performed as defined for the EoT examination. With the subject's agreement, the Investigator and/or Sponsor may request additional (or fewer) assessments in accordance with Appendix 4.

If not scheduled on the day of early termination and if possible, a PK sample should be collected.

6.1.5 Criteria for withdrawal

A subject may terminate participation in the trial at any time without providing a reason and without any personal disadvantage. Additionally, the Investigator may discuss the removal of a subject with the AiCuris Responsible Physician at any time. Subjects who are withdrawn from the trial are not allowed to re-enter at a later date.

A subject may be withdrawn from the trial under the following circumstances:

- Subject's decision
  - Withdrawal of consent at any time, without the need for explanation
- Investigator's decision
  - For any reason considered to be in the best interest for the safety of the individual or in the safety interest of the other subjects
- Sponsor's / Risk Benefit Committee's (RBC) decision
  - Protocol violation
  - Administrative reasons
  - Any other valid and ethical reason
  - Termination of the trial

Additional withdrawal criteria include:

- AE warranting withdrawal
- Use of/need for a prohibited medication which in the opinion of the Sponsor or Investigator may jeopardize the trial results or represent a risk to the subject
- Pregnancy (in this case, the subject is to be followed up until delivery or abortion)
- In case of non-compliance with trial procedures or restrictions.
- Subject meets the individual rules criteria (see Appendix 2)

If a subject withdraws consent, no further investigation or treatment may be performed. The Investigator will explain to the subject that data already collected will be analyzed.

The EoT evaluations are to be performed to ensure subject safety (see Section 6.1.3). If possible, when trial medication is withdrawn, but the subject has not withdrawn consent from trial participation, all scheduled visits should continue to be performed as planned, and all SAEs must

be reported until the EoT Visit. All documentation concerning the subject must be as complete as possible.

The reason for discontinuation of trial medication or withdrawal from the trial must be clearly documented in the eCRF.

Withdrawals due to non-attendance must be followed up by the Investigator to obtain the reason for non-attendance.

In addition, the Investigator must prepare a detailed written explanation for AiCuris/ and the Ethics Committee (EC) where applicable. AiCuris must be informed as soon as possible about the withdrawal of a subject from the trial.

6.1.6 Stopping criteria

Premature termination of the trial

The Sponsor has the right to close this trial at any time. The Principal Investigator is authorized to set the trial on hold at any point of time if the safety of subjects is endangered. Specifically, the trial will be terminated prematurely if:

- New toxicological or pharmacological findings or SAEs invalidate the earlier positive benefit-risk-assessment
- AEs occur in such prominence (ie, intensity and frequency) that a continuation of the trial is no longer justified, see also Appendix 2.
- The Sponsor decides to discontinue the clinical trial.

6.2 Treatments

There are 4 IMPs in this clinical trial:

- Pritelivir 100 mg tablets
- Matching placebo to Pritelivir 100 mg tablets
- Encapsulated moxifloxacin tablets 400 mg
- Matching placebo to encapsulated moxifloxacin tablets 400 mg

6.2.1 Route and administration

Pritelivir

Pritelivir will be administered orally as Pritelivir 100 mg tablets.

In Group 1: A loading dose of 400 mg on Day 1, followed by a once daily 100 mg dose regimen from Day 2 to Day 6, followed by a once daily 400 mg dose regimen from Day 7 to Day 16.

Pritelivir placebo

Pritelivir placebo will be administered orally as Pritelivir placebo tablets.

In Group 2: The same number of corresponding pritelivir placebo tablets will be administered from Day 1 to Day 16 in Group 2 as verum tablets in Group 1.

Moxifloxacin and moxifloxacin placebo

A single oral dose of moxifloxacin placebo will be administered in Group 1 on Days 2 and 17 as well as on Day 17 in Group 2a and Day 2 in Group 2b.

A single oral dose of 400 mg moxifloxacin will be administered in Group 2a on Day 2 and in Group 2b on Day 17.

Over-encapsulated moxifloxacin- and matching placebo will be used to maintain double-blindness.

6.2.2 Selection of doses

Pritelivir

The most current ICH E14 guideline 'Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs' [3, 4] states the following: "If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure". Thus, a high supra-therapeutic dose of pritelivir, which results in an exposure in excess of what would be observed in patients, will be used in this TQT trial. In addition, a dose that produces a therapeutic exposure will be investigated.

Therapeutic dose:

Pritelivir has already entered Phase 3 development stage and the therapeutic dose for pritelivir in the currently ongoing Phase 3 trial is 100 mg/day. Therefore, this is also the planned therapeutic dose for this TQT trial.

Due to the long terminal elimination half-life, a loading dose of 400 mg will be administered on Day 1 to reach steady-state conditions immediately. This will also guarantee steady-state conditions on the planned PK- and ECG-Day 6.

Supra-therapeutic dose:

Following the exposure to 400 mg pritelivir on Day 1 and 100 mg qd for the next 5 days, dosing of 400 mg qd pritelivir for 10 further days (Day 7 to Day 16) is sufficient (based on results of trial AIC316-01-I-05) to reach steady-state conditions for the planned pharmacokinetic sampling and ECG Day 16.

Overall, a dosage of 400 mg qd pritelivir is considered to be the supra-therapeutic dose because of a lag of absorption at doses higher than 400 mg pritelivir, ie, no higher exposures can be reached by increasing the dose when administering pritelivir once daily.

After single- and multiple-dose administration, there was a dose-proportional increase of the area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) between 5 mg and 480 mg and in peak plasma concentration (C_{max}) between 5 mg and 400 mg. Higher doses of pritelivir did not further increase systemic exposure, suggesting that the lack of dose proportionality may be related to capacity-limited absorption (as opposed to non-linearity in elimination). An about 4-fold higher exposure after 400 mg qd dosing compared to the therapeutic exposure after 100 mg qd dosing is also considered to cover intrinsic and extrinsic factors that may increase pritelivir exposure after a therapeutic dose of 100 mg pritelivir is given

once daily. Due to pritelivir's main metabolism pathway (hydrolysis), potential drug-drug-interaction effects to increase pritelivir exposure eg, by inhibiting CYPs are negligible. Further, food has no relevant effect on $AUC_{0\text{-last}}$ and leads only to a mild increase in C_{max}. Moreover, the absorption from gut cannot be increased much as the absolute bioavailability is already high (>70%). The influence of hepatic and renal impairment is currently under investigation in parallel clinical trials, but no relevant effects are expected.

Safety wise, the 400 mg once daily dose is discussed in the risk/benefit assessment, Section 2.3.

Moxifloxacin

A single dose of 400 mg moxifloxacin will be administered in this trial to demonstrate the trial's ability to detect a small effect on the QT interval (assay sensitivity). This dose is the standard dose in TQT trials [1].

6.2.3 Description of investigational product

Pritelivir 100 mg tablets

Pritelivir 100 mg tablets are provided as film-coated tablets for oral administration.

Pritelivir 100 mg tablets were manufactured in accordance with Good Manufacturing Practice by:

Rottendorf Pharma GmbH
Ostenfelder Str. 51-61,
59320 Ennigerloh, Germany

Pritelivir 100 mg tablets are temporarily stored, by:

Almac Clinical Services Limited
Seagoe Industrial Estate 9
Charlestown Road Craigavon
Northern Ireland
BT63 5PW, United Kingdom

Pritelivir 100 mg tablets are packed, stored and QP released by:

Richmond Pharmacology Ltd
1A Newcomen Street
London Bridge
London SE1 1YR

Pritelivir placebo tablets

Pritelivir placebo tablets are provided as film-coated tablets for oral administration.

Pritelivir placebo tablets were manufactured in accordance with Good Manufacturing Practice (GMP) by:

Rottendorf Pharma GmbH
Ostenfelder Str. 51-61,
59320 Ennigerloh, Germany

Pritelivir placebo is temporarily stored, by:

Almac Clinical Services Limited
Seagoe Industrial Estate 9
Charlestown Road Craigavon
Northern Ireland
BT63 5PW, United Kingdom

Pritelivir placebo are packed, stored and QP released by:

Richmond Pharmacology Ltd
1A Newcomen Street
London Bridge
London SE1 1YR

Moxifloxacin capsules

Moxifloxacin is commercially available as 400 mg tablets and will be procured and encapsulated in gelatin capsules for oral administration. The encapsulated moxifloxacin formulation was manufactured in accordance with GMP by:

Patheon by Thermo Fisher Scientific,
151 Brook Drive,
Milton Park,
Abingdon, Oxfordshire,
OX14 4SD, United Kingdom

Encapsulated moxifloxacin tablets 400 mg are packed, stored and QP released by:

Richmond Pharmacology Ltd
1A Newcomen Street
London Bridge
London SE1 1YR

Matching placebo to encapsulated moxifloxacin tablets 400 mg

Moxifloxacin placebo is an identical capsule size (to that of Moxifloxacin encapsulated tablets) containing one of the excipients present in the Moxifloxacin tablet. The placebo tablet will be composed of 75% MCC PH200 and 25% Dicalcium phosphate (A-Tab) and encapsulated in gelatin capsules.

Matching placebo to encapsulated moxifloxacin tablets 400 mg was manufactured in accordance with GMP by:

Patheon by Thermo Fisher Scientific,
151 Brook Drive,
Milton Park,

Abingdon, Oxfordshire,
OX14 4SD, United Kingdom

Matching placebo to encapsulated moxifloxacin tablets 400 mg are packed, stored and QP released by:

Richmond Pharmacology Ltd
1A Newcomen Street
London Bridge
London SE1 1YR

6.2.3.1 Drug accountability

A Drug Accountability Form will be developed for use within the trial which will allow the accurate and reliable tracking of trial medication.

The Investigator's duties for drug accountability may be designated to an appropriate pharmacist or another appropriate individual who is under supervision of the Investigator.

The Investigator or appropriate designee is obliged to keep documentation (eg, site specific drug accountability log, trial medication dispensing log) of the delivery, use, and destruction or return of unused, used or partially used, packages of trial medication. The documentation must include dates, quantities, lot/batch/serial numbers or other identification numbers, and the means to identify the subject to whom a specific trial medication was dispensed, eg, subject number.

Before any trial medication is destroyed or returned by the site to a central facility, the Investigator must allow the Clinical Research Associate to perform drug reconciliation. Entries in the electronic data capture (EDC) and other accountability records will be compared with the returned and residual trial medication, with clarification of any discrepancies or inconsistencies.

IMP must not to be used for any purpose other than the present trial. Remaining IMP must be destroyed by the site at the end of the trial.

6.2.3.2 Storage conditions and stability

Pritelivir 100 mg tablets

At all storage locations during packaging, labeling and distribution, temperature logs and documentation about the receipt and shipment of trial medication will be maintained.

Pritelivir 100 mg tablets will be stored in a secure location with restricted access at room temperature between 15 and 30°C. The storage conditions at the investigational sites will be recorded daily, and documentation about drug accountability (receipt and dispense) will be maintained.

Pritelivir placebo tablets

At all storage locations during packaging, labeling and distribution, temperature logs and documentation about the receipt and shipment of trial medication will be maintained.

Pritelivir placebo tablets will be stored in a secure location with restricted access at room temperature between 15 and 30°C. The storage conditions at the investigational site will be

recorded daily, and documentation about drug accountability (receipt and dispense) will be maintained.

Moxifloxacin capsules

Moxifloxacin capsules (400 mg) will be stored according to the local pharmacy procedures and the Summary of Product Characteristics. The encapsulated tablets will be stored between 15 and 25°C.

Moxifloxacin matching placebo capsules

Moxifloxacin placebo capsules will be stored according to the local pharmacy procedures and the Summary of Product Characteristics. The encapsulated tablets will be stored between 15 and 25°C.

6.2.4 Concomitant medications

Concomitant medication is prohibited throughout the trial, except for hormonal contraception and hormone replacement therapy as well as single intake of a drug if judged by the Investigators to have no clinical relevance and no relevance for the trial objectives. Limited amounts of paracetamol (not exceeding 2 g per day) are allowed on demand to treat painful intercurrent adverse events (eg, headache, migraine). The need for other medication may lead to subject's withdrawal from the trial. In any case, the Investigator will inform the Sponsor about the concurrent medication given.

Details of all prior and concomitant medications should be recorded by the Investigator on the eCRF and source record.

Restrictions concerning pre-trial or concomitant medication use are given in the exclusion criteria in Section 5.2.

6.2.5 Dietary and other restrictions

Dietary restrictions

Whenever subjects are confined in the ward, only the drinks and meals provided by the trial personnel will be allowed.

For whole Day -1 time points, they should be approximately the same as the planned time for ECGs on Days 1, 2, 6, 16 and 17.

Meals

- On Days -1, 1, 2, 6, 16 and 17, in order to omit the effect of food subjects will fast from at least 10 h before until 4 h after dosing to have the same conditions on all Holter-ECG days. On all other days between Day 3 and 15 (except Day 6), subjects will be dosed 2 h after a standardized continental breakfast. On Days 18 to 20 subjects will receive a standardized continental breakfast in the morning.

- On Days -1, 1, 2, 6, 16 and 17, the same meal will be served (an identical percentage of fat, proteins, and carbohydrates) for all subjects: lunch 4 h (600-800 calories), afternoon snack 7 h, and dinner 11 h after drug administration. On the other days between Day -1 and 17, standardized meals will be served (lunch 4 h, afternoon snack 7 h, dinner 11 h post-dose). On Days 18 to 19 lunch, afternoon snack, and dinner will be served at a comparable time to that of Days -1 to 17.

Fluids

- On Days -1, 1, 2, 6, 16 and 17, intake of any fluids other than those provided by the trial personnel for drug administration will not be allowed from at least 1 hour before until 4 h after dosing. From 4 to 24 h after drug administration non-carbonated/carbonated water at room or refrigerator temperature is allowed in a total amount over 24 h post-dose of up to 2.5 L.
- On the Days 3 to 5 and 7 to 15, only fluid intake of non-carbonated/carbonated water at room or refrigerator temperature up to a total amount over 24 h of 2.5 L is allowed, which will be provided by the trial personnel.
  There will be no restrictions with regard to the amount of fluids during Days 18 to 20. However, enzyme activity influencing fluids or beverages (eg, but not limited to grapefruit juice and tonic water) are not allowed during the in-house period.

Alcohol

- Subjects will not be allowed to consume alcohol within 2 days before confinement until discharge and within 2 days prior to the post-trial examination (14 to 21 days after last dosing).

Further details are provided in the SOM.

Other restrictions

- Subjects will not be allowed to perform exhausting exercise (eg, competitive sports or weightlifting) within 4 days before confinement until the End of Trial examination
- Subjects will not be allowed to smoke during the in-house period.
- During the in-house periods subjects will preferably remain inside the ward building. Light outside activities under supervision of site staff, eg, going for a walk, will be permitted, however.

Further restrictions are given in the exclusion criteria in Section 5.2

6.2.6 Treatment compliance

All trial medication administrations will be performed by the Investigator or appropriately trained designee (for example a Research Physician) and the dosing will be verified by another member of the Investigator's staff. After oral administration, a thorough hand and mouth check will be performed to ensure proper oral ingestion of the trial medication.

The blood concentrations of pritelivir and moxifloxacin will serve as an additional measure of treatment compliance.

Pritelivir, moxifloxacin and respective placebo are planned to be administered orally as detailed in Table 6-1.

Table 6-1 IMP or placebo for each anticipated dose level

Cohort	Treatment	IMP/Placebo dispensed	Administration
Group 1	400 mg or 100 mg pritelivir	4 or 1 x 100 mg pritelivir tablet	Study treatments will be administered to each participant with 240 mL of water
	Moxifloxacin placebo	1 x matched placebo to moxifloxacin capsule	
Group 2a and 2b	Pritelivir placebo	4 or 1 x matched placebo to pritelivir tablet(s)	
	400 mg Moxifloxacin	1 x 400 mg moxifloxacin capsule	
	Moxifloxacin placebo	1 x matched placebo to moxifloxacin capsule	

Detailed instructions for dose administration will be included in the SOM.

6.3 Assignment of subjects to treatment groups

Subjects will be randomly assigned to Group 1, Group 2a, or Group 2b at a 2:1:1 ratio. All subjects in this trial will be assigned to a treatment regimen according to a randomization schedule generated by a statistician using PROC Plan.

Details regarding the unique screening and subject number will be included in the SOM.

6.4 Blinding

Subjects and all trial personnel, except for pharmacy staff at Richmond Pharmacology, and A&M for assignment of bioanalytical samples, will be blinded with respect to the assignment to group 1 (pritelivir) and 2 (matched placebo to pritelivir) as well as the treatment sequence of moxifloxacin and respective matching placebo in group 2. To maintain blinding, matching placebos (pritelivir or moxifloxacin, as appropriate) will be used at equivalent timepoints to verum treatment in other treatment sequences, so that all subjects receive the same number of tablets or capsules, with the same appearance, at equivalent timepoints in their respective treatment sequence.

6.4.1 Maintenance of randomization code blinding

The pharmacy staff preparing the IMP will not be blinded to trial drug assignment. During the trial, the individual randomization codes will be kept in the site's clinical trials pharmacy, accessible to the pharmacy personnel only. Upon completion of the trial, after the database lock and after the blind is revealed, the randomization list will be filed in the Trial Master File.

Administrative and operational staff of the trial site, including Principal Investigator and trial manager as well as monitors, AiCuris staff and data managers will remain blinded during the course of the trial until Database Lock and finalization of the Statistical Analysis Plan.

6.4.2 Procedure for unblinding individual randomization codes

In the event of an emergency, an envelope for each subject containing his/her trial drug assignment will be available in the pharmacy at the clinical trial site. Unblinding should only be considered for the safety of the subject. If unblinding is deemed necessary by the Investigator, the Investigator or designee can unblind the subject's treatment allocation using the envelope available from the pharmacy. The Investigator or designee must note the date, time, and reason for unblinding and inform the Sponsor of unblinding as soon as practicably possible.

6.5 Expected duration of subject participation

The maximum total period of subject participation in the trial will be 58 days from Screening, through Admission, inpatient treatment period, outpatient treatment period and up to the EoT safety follow-up visit:

Screening period	Day -21 to Day -1	21 days
Treatment period (inpatient)	Day 1 to Day 20	20 days
Follow-up period (to EoT)	Up to Day 30 to 37	17 days
Total duration of participation		58 days

6.6 Trial assessment methods

Note: Times relative to trial treatment administration refer to the time of tablet/capsule administration.

Considering priorities and order of procedures, the design of the Master Treatment Schedule (MTS) requires scheduling time windows for those tasks that occur at the same protocol time point but need to be performed before or after the priority task. The permitted time windows are set out in the Data Handling Protocol for Scheduling Time Windows (DHP STW).

Clinical assessments should be performed exactly at the time prescribed in the MTS.

Deviations:

- Deviation from scheduled time in MTS: If the time of clinical assessment deviates from the time prescribed in the MTS, a clinical comment should be made in the appropriate source data/eCRF space that a deviation from the MTS occurred. The following deviations from the MTS do not require a comment:

  All Procedures ±2 mins

- Deviation from scheduling time window in DHP STW: If the time of clinical assessment deviates from the scheduling time window in the DHP STW, this will be considered a protocol deviation. These deviations will be identified, classified (minor, major, critical), and managed in accordance with the DHP STW.

Sequence of procedures

When the protocol's Schedule of assessments requires that multiple procedures occur at the same timepoint, PK blood sampling takes priority and is to be scheduled at the exact time point defined in the Schedule of assessments.

If 2 or more measures or actions coincide, they should be performed according to the preferred sequence:

Pre-dose in-house

1. ECG (measured after rest of at least 10 minutes in supine position)
2. Vital Signs (measured after rest of at least 5 minutes in supine position)
3. Blood Samples (PK>clinical chemistry and hematology)
4. PGx sample
5. Breakfast

Post-dose in-house

1. ECG (measured after rest of at least 10 minutes in supine position)
2. Vital Signs (measured after rest of at least 5 minutes in supine position)
3. Blood Samples (PK (exactly on time) >clinical chemistry and hematology)
4. Food

Post-dose outpatients

1. ECG (measured after rest of at least 10 minutes in supine position)
2. Vital Signs (measured after rest of at least 5 minutes in supine position)
3. Blood Samples (on time) (PK>clinical chemistry and hematology)

6.6.1 Demographics and subject characteristics

The following demographic parameters will be recorded for the demographic assessments: age, sex, height, weight, and ethnicity (including race).

Further, information on lifestyle and habits (eg, smoking, alcohol consumption) and medical history records will be provided.

6.6.2 Efficacy

Not applicable.

6.6.3 Pharmacokinetics

Detailed instructions on sample collection and processing are described in the specific laboratory manual.

Actual sampling times will be recorded in the eCRFs.

Blood sampling

Unless indicated, any sample taken outside the acceptable blood sampling time windows listed above will be considered a time deviation even if the deviation should be pharmacokinetically irrelevant.

Each blood sample will be labeled to indicate the trial code, subject number, and nominal sampling time.

The total volume of blood planned to be withdrawn from each subject is unlikely to exceed 300 mL over the duration of the trial (including safety laboratory, PK sampling, genotyping sampling) but will in any event be less than standard blood donation.

6.6.3.1 Collection and handling of plasma samples

Pritelivir and metabolites in plasma

For determination of pritelivir (total), as well as the metabolites AIC090015 and AIC090105, 3 mL of blood will be drawn by venous puncture or indwelling venous catheter into appropriate blood collection tubes to prepare plasma sample determinations.

Blood sampling for determination of pritelivir, AIC090015 and AIC090105 concentrations in plasma will be carried out on:

- Day 1: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h post-dose (ie, Day 2 pre-dose)
- Day 3 to 5: pre-dose (trough),
- Day 6: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h post-dose (ie, Day 7 pre-dose),
- Day 13 to 15: pre-dose (trough),
- Day 16: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h post-dose (ie, Day 17 pre-dose).

Moxifloxacin in plasma

For determination of moxifloxacin in plasma, 2.7 mL of blood will be drawn by venous puncture or indwelling venous catheter into appropriate blood collection tubes to prepare plasma sample determinations.

Blood sampling for determination of moxifloxacin plasma concentrations will be carried out on:

- Day 2: pre-dose, 1, 2, 3, 4, 5, 6, 7 and 8 h post-dose,
- Day 17: pre-dose, 1, 2, 3, 4, 5, 6, 7 and 8 h post-dose.

6.6.3.2 Analytical methods

Validated methods will be used to determine the concentrations of the analytes: pritelivir, AIC090015, AIC090105, and moxifloxacin.

6.6.3.3 Pharmacokinetic parameters

Plasma concentrations will be determined by A&M and communicated to Venn Life Sciences for derivation of pharmacokinetic parameters by a non-compartmental analysis. Venn Life Sciences will provide the calculated PK parameters to Richmond Pharmacology for incorporation into the final data set, as well as to AiCuris for preliminary evaluation.

The pharmacokinetic analysis will be performed under the responsibility of the Sponsor according to AiCuris Standard Operating Procedure "Analysis of pharmacokinetic data".

The PK variables will be derived based on the plasma concentrations of the analytes (see Section 6.6.3.1) and the actual sampling times, using non-compartmental methods.

The PK endpoints are defined in Section 8.3. Additional PK parameters may be examined as deemed necessary.

6.6.3.3.1 Definitions and calculations of pharmacokinetic variables

The definitions and methods of calculation of the pharmacokinetic parameters are as follows:

C_{max}	Maximal observed analyte concentration
$C_{max,ss}$	Maximal observed analyte concentration at steady state
C_{min}	Minimum observed analyte concentration
$C_{av,ss}$	Average concentration at steady state, calculated as: $AUC_{\tau,ss}/\tau$
C_{0h}	Drug concentration observed at the last planned timepoint prior to dosing
t_{max}	Time to reach the maximal observed analyte concentration
t_{lag}	Time period between the time of dosing and the time of the first measurable concentration
AUC_{τ}	Area under the analyte vs. time concentration curve over a dosing interval τ after the starting dose during multiple dosing, calculated by linear up/ln down summation.
$AUC_{\tau,ss}$	Area under the analyte vs. time concentration curve over a dosing interval τ at steady-state (ss), calculated by linear up/ln down summation.
CL/F	Total apparent clearance of drug following single extravascular dose administration calculated as: $CL/F = Dose / AUC_{0-\infty}$
CL_{ss}/F	Apparent clearance of drug at steady state following extravascular dosing, calculated as: $CL_{ss}/F = Dose / AUC_{\tau,ss}$
$t_{1/2z}$	The apparent terminal elimination half-life calculated as: $t_{1/2z} = 0.693 / \lambda_z$

λ_z	The apparent terminal elimination rate constant, determined by linear regression of terminal points of the ln-linear analyte concentration-time curve.
V_d/F	Apparent volume of distribution after a single dose e.v. administration calculated as: $V_d/F = Dose_{e.v.} / (\lambda_z \cdot AUC_{0-\infty})$
$V_{d,ss}$	The apparent volume of distribution at steady state of distribution, calculated as: $V_{d,ss}/F = MRT \cdot CL_{ss.} / F$
MRT	Mean residence time is the time corresponding to the time (average time) the number of molecules absorbed reside in the body, calculated by: $MRT = AUMC / AUC$

The following requirements are to be met for an acceptable calculation of $t_{1/2z}$, λ_z, $AUC_{0-\infty}$, CL/F, V_d/F and MRT:

a. at least 3 data points are used in the calculation (not including C_{max}), otherwise $t_{1/2z}$, λ_z, and (consequently) $AUC_{0-\infty}$, CL/F, V_d/F and MRT are not assessable (NA)
b. coefficient of determination (r^2_{adj}) is at least 0.850
c. the span of time points (λ_z upper - λ_z lower) used in the calculation is at least twice the calculated $t_{1/2z}$

If requirement b or c is not met, λ_z, $t_{1/2z}$, $AUC_{0-\infty}$, CL/F, CL_{ss}/F, V_d/F, $V_{d,ss}$/F and MRT will be reported as approximations and will be excluded from the descriptive statistics.

$AUC_{0-\infty}$ (and consequently CL/F, CL_{ss}/F, V_d/F, $V_{d,ss}$/F and MRT) will also be reported as approximations in case the $AUC_{0-\infty,ex}$ (the part of $AUC_{0-\infty}$ that is calculated by extrapolation) exceeds 20.00%, but will be excluded from the descriptive statistics and from statistical analysis.

6.6.4 Safety

6.6.4.1 Adverse events

Subjects will be interviewed by trained clinic personnel using non-leading questions (eg, "How do you feel?") to elicit information on possible adverse events within 30 minutes prior to administration or assessment at:

- Screening: Day -2, -1,
- Days 1 to 17 (pre-dose),
- Day 18 to 20, and
- EoT.

Spontaneously reported and inquired adverse events will be recorded in an AE log. In case of adverse events, the Investigator may decide to repeat a clinical examination and/or laboratory test.

6.6.4.1.1 *Definition of adverse event*

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

During a trial, an AE can also occur at times when IMP(s) is (are) not taken, eg, during wash-out periods or during a placebo run-in.

6.6.4.1.2 *Definition of adverse drug reaction*

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

6.6.4.1.3 *Definition of serious adverse events or serious adverse drug reactions*

An SAE or serious adverse drug reaction (SAR, which is an SAE that has been assessed as being causally related to IMP) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening [1]
- Requires hospitalization or prolongation of existing hospitalization [2]
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect, or
- Is another medically important event or reaction [3]

6.6.4.1.4 *Definition of intensity of adverse events*

The following categories will be used for the rating of intensity according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

---

[1] The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe.

[2] Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (eg, for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of IMP and which has not increased in severity or frequency.

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

(Corrected Version 2.1, July 2017, see Appendix 1). In addition, all deaths related to an AE are to be classified as Grade 5.

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

6.6.4.1.5 Definition of adverse event causality

A determination of the relationship between an AE and the IMP must be made after due consideration by the Investigator for each AE.

The assessment of the relationship of an AE to the administration of IMP is a clinical decision based on all available information at the time of and after the occurrence of the event. The factors which may be considered when evaluating the relationship of an AE to the IMP, include: time from exposure to IMP until onset of the event; recovery or improvement on discontinuation of IMP; availability of alternative explanations such as underlying or intercurrent diseases; concomitant medications or treatments; pharmacology and pharmacokinetic of the IMPs; known response pattern for this class of drug; recurrence on reintroduction of the IMP.

The relationship of adverse events to the IMP will be assessed according to the following categories:

- **"definite"**: A clinical event, including laboratory test abnormality, with a reasonable temporal relationship to drug administration. AE cannot be explained by concomitant diseases or other drugs or chemicals. Response on drug withdrawal must be clinically explicable. AE must be pharmacologically or phenomenologically unambiguous; a satisfactory rechallenge procedure might be used.
- **"probable"**: A clinical event, including laboratory test abnormality in a reasonable time sequence to administration of the drug. AE is unlikely to be attributed to concurrent disease or other drugs or chemicals and follows a clinically reasonable response on withdrawal; information about rechallenge is not required.
- **"possible"**: A clinical event, including laboratory test abnormality in a reasonable time sequence to administration of the drug, but AE could also be explained by concurrent diseases or other drugs or chemicals; information on drug withdrawal may be lacking or unclear.
- **"unlikely"**: A clinical event, including laboratory test abnormality, with a weak temporal relationship to drug administration. Other factors, such as the underlying, concomitant diseases, concomitant medication, are plausible to have contributed to the event.

- **"not related"**: No relationship to administration of trial drug, ie, there is a clear alternative explanation, an unreasonable temporal relationship between the drug and the event, or relationship is otherwise not plausible.

6.6.4.1.6 Definition of adverse event outcome

The outcome of adverse events will be described according to the following 6 categories:

1. Resolved
2. Resolving
3. Not Resolved
4. Resolved with sequelae
5. Fatal
6. Unknown

6.6.4.1.7 Definition of expectedness

An adverse reaction, the nature and intensity of which is consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP) is considered as expected. The Investigator's Brochure, Section 6.5, Reference Safety Information, will serve as the reference document for the assessment of expectedness on pritelivir in this clinical trial. The moxifloxacin SPC will serve as the reference document for the assessment of expectedness on moxifloxacin. The expectedness is determined by the Sponsor.

6.6.4.1.8 Adverse event recording and reporting

Period of recording

The period of recording of AE or SAE will last from the time that the subject signs the Informed Consent Form to the last trial day according to the Clinical Trial Protocol, regardless of the relationship to IMP. This includes events that occur at times when IMP(s) is (are) not taken, eg, during wash-out periods or during a placebo run-in. If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical trial in a subject treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

Follow-up of subjects with an adverse event

AEs and SAEs have to be followed up until their resolution, they have become stable, returned to Baseline condition or can be explained by other causes (eg, concomitant symptom or disease) and clinical judgment indicates that further follow-up is not warranted.

Adverse event recording

Each AE and SAE occurring to a subject, either spontaneously revealed by the subject or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the IMP, must be recorded on the AE information page of the eCRF and in the subject's source data.

The following aspects of AE/SAEs will be documented by the Investigator in the source data as well as on the eCRF:

- If possible, diagnosis or syndrome, otherwise each single symptom.
- Date and time of onset and end of AE/SAE.
- Seriousness
  (serious/ non-serious).
- Intensity using the Grading of the Severity of Adverse Events according to the DAIDS
  (mild/ moderate/ severe/ potentially life-threatening/ fatal, Section 6.6.4.1.4).
- Causal relationship with IMP
  (definite/ probable/ possible/ unlikely/ not related, Section 6.6.4.1.5).
- Outcome
  (resolved/ resolving/ not resolved/ resolved with sequelae/ fatal/ unknown, Section 6.6.4.1.6).
- Treatment of event, if applicable
  (eg, any medication as well as any other medical measures).
- Actions taken regarding IMP
  (withdrawn, dose reduced, dose increased, dose not changed, unknown, not applicable).

Changes in intensity of an AE should be recorded as a separate AE with a new onset. If an AE becomes serious, a new AE has to be recorded flagged as serious and additionally a SAE form has to be completed with a new onset.

Adverse event reporting

The Investigator must report to the Sponsor all AEs, which occur during the clinical trial, regardless of their relationship to the IMP by documentation in the EDC.

Serious adverse event reporting

AiCuris has contracted IQVIA as an external service provider for pharmacovigilance. SAEs will be reported by the Investigator to IQVIA immediately (without undue delay) after becoming aware of occurrence. IQVIA in turn must promptly report SAEs to AiCuris being the primary responsible body for pharmacovigilance.

SAEs must be reported using the eCRF. It has to be ensured that all other relevant information has been included (eg, relevant medical history, concomitant medications, laboratory tests, examinations). A paper SAE report Form must also be completed in case the eCRF system is not available. The original copy of the SAE Report Form and the fax confirmation sheet or email must be kept at the trial site.

The contact details for IQVIA are:

IQVIA
Eastpoint Business park, Fairview
Dublin 3 Ireland

Phone:
Email:
IQVIA Safety Fax: [redacted]

The following information will be available in the SAE report:

- Trial Protocol number
- Status of report: initial, follow-up
- Subject identification number
- Subject demographics
- IMP:
    - Drug code, kit number, or name (if applicable)
    - Batch number (if applicable)
    - Start and end date, dose – if known
- Nature of the AE including date of onset, intensity, and treatment (including hospitalization)
- Action taken with respect to IMP
- Causal relationship to IMP(s) in the opinion of the Investigator
- Previous and concomitant diseases
- Previous and concomitant drug therapy
- Outcome
- Recovery date (if available)
- In the case of death, the cause and post-mortem findings.

The Investigator will fill in the Serious Adverse Event Form in English for reporting.

Follow-up reports relating to the subject's subsequent course must be submitted to IQVIA responsible for SAE management using the eCRF until the event has subsided or the condition stabilized and be sufficiently medically explained. A paper SAE report Form must also be completed for submission by fax or email in case the eCRF system is not available.

In case of death the Investigator must submit to IQVIA by fax or email all relevant follow-up-information that can be obtained (anonymized autopsy findings, clear photocopies of hospital records, consultant report[s]) within 24 h of receipt of the information.

Suspected Unexpected Serious Adverse Reactions reporting

Any adverse reaction that is serious and unexpected (SUSARs) has additional reporting requirements, as described below:

- If the SUSAR is fatal or life-threatening, Regulatory Authorities (RAs), EC and Investigators will be notified immediately, but at the latest within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, hospital report) information should be reported to the Competent Authorities (CAs), and Investigators within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, RAs, EC and Investigators will be notified immediately, but at the latest within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the Investigator of relevant information about SUSARs that could adversely affect the safety of subjects in a timely fashion. Follow-up information may be submitted if necessary.

In case of occurrence of any new event or other safety issue relating to the conduct of the trial or the development of the IMP where that new event is likely to affect the safety of the clinical trial subjects, the Sponsor and the Investigator must take appropriate urgent safety measures to protect the subjects against any immediate hazard. The Sponsor has to inform the concerned CA of those new events and the measures taken. That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

6.6.4.1.9 Other safety issues, which might alter the benefit-risk assessment of the investigational drug

Other safety issues which might alter the current benefit-risk assessment of the investigational drug or which would be sufficient to consider changes in the investigational drug administration or in the overall conduct of the trial must be reported to the CA and the EC as soon as possible but no later than 15 calendar days after the Sponsor has first knowledge of them. Further relevant follow-up information should be given as soon as possible.

Such safety issues may be:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important,
- Post-trial SUSARs that occur after the subject has completed a clinical trial and are reported by the Investigator to the Sponsor,
- Events relating to the conduct of the trial or the development of the Investigational Medicinal Product likely to affect the safety of the subjects.

Investigators will be informed accordingly.

6.6.4.1.10 Annual Safety Report

The Sponsor will also provide annual safety updates once a year throughout the clinical trial or on request to the RAs responsible for the trial. These updates will include information on SAR (including SUSAR) which occurred in the clinical trial and other relevant safety findings.

6.6.4.1.11 Procedures in case of pregnancy

All pregnancies that occur during the trial in female subjects and female partners of male subjects should be followed up. If such a pregnancy occurs, a Drug Exposure via Parent form has to be completed and sent to IQVIA:

Fax: [redacted]

The contact details for IQVIA are:

IQVIA
Eastpoint Business Park, Fairview
Dublin 3
Ireland

Phone:
Email: [redacted]

6.6.4.2 Safety laboratory parameters, alcohol breath test, drug test, and pregnancy test (females only)

Laboratory parameters are listed in Table 6-2.

Blood and urine samples remaining after clinical laboratory assessments have been performed will not be stored for future use and will be destroyed after analysis as per laboratory procedure.

Safety laboratory parameters will be assessed in fasted state at:

- Screening (between Day -21 and -3),
- Day -2 (Admission),
- Pre-dose on Days 6, 16, and 20,
- EoT.

Table 6-2 Laboratory parameters

Serum chemistry

AST ALT GGT alkaline phosphatase total bilirubin direct bilirubin cholesterol triglycerides creatine phosphokinase (CK) CK-MB, if CK is elevated	LDH amylase lipase creatinine uric acid urea albumin total protein	potassium sodium calcium chloride inorganic phosphate ferritin transferrin thyroxin TSH glucose (fasting at End of Trial) CRP

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CK=creatine phosphokinase; CRP=C-reactive protein; GGT=gamma-glutamyltransferase; LDH=lactate dehydrogenase; TSH=thyroid stimulating hormone

Hematology and coagulation parameters

hemoglobin hematocrit erythrocytes MCH	MCV MCHC white blood count differential blood count	platelets PT PTT INR fibrinogen

INR=international normalized ratio; MCH=mean cell hemoglobin; MCHC=mean cell hemoglobin concentration; MCV=mean cell volume; PT=prothrombin; PTT=partial thromboplastin time

Serology (only at Pre-Trial examination)

HIV-I- and -II-antibody	HbsAg	anti-HBc (IgG + IgM) anti-HCV

HBc=hepatitis B core; HBsAg=hepatitis B antigen; HCV=hepatitis C virus; IgG/M=immunoglobulin (class G/M)

Urinalysis

pH glucose proteins ketones bilirubin	urobilinogen nitrite blood leucocytes	urine sediment [a)]

a) In case of out-of-range findings in the urinalysis

Note: All baseline parameters (taken at Screening and Day -2) have to be available and judged prior to dosing on Day 1.

SARS-CoV-2 testing

Subjects must also comply with the latest COVID-19 safety measures/ testing applicable at the site at that time, for entry into the unit and during in-house stays.

Note:

COVID-19 tests will be carried out at regular intervals, prior to entry in the unit and throughout the residential period as per the latest Richmond Pharmacology COVID-19 Infection Control Guidelines and pre-entry algorithms.

Tests for pregnancy and postmenopausal status

Pregnancy testing (women)

A serum β-HCG (beta-human chorionic gonadotropin) test will be performed at:

- Screening (between Day -21 and -3) and
- EoT

A urine β-HCG test will be performed on:

- Day -2 (Admission).

Postmenopausal status (women of non-childbearing potential)

An FSH test will be performed for women of non-childbearing potential who have a history of no menses of at least 24 months at:

- Screening (between Day -21 and -3).

Tests for drug and alcohol abuse

A urine sample will be tested for drugs (benzodiazepines, opiates, amphetamines, methadone, cocaine, cannabinoids, barbiturates, cotinine) and an alcohol breath test will be performed at:

- Screening (between Day -21 and -3) and

- Day -2 (Admission).

6.6.4.3 ECG

6.6.4.3.1 Holter-ECG

A Screening Holter will be performed at Screening.

From 1 hour prior to dosing until 8 h (Day 2 and Day 17) or 24 h (Day -1, 1, Day 6 and Day 16) after dosing, a Holter-ECG will be carried out in all subjects. Holter-ECGs will be recorded using high-resolution 12-channel Holter recorders recorded in parallel to bedside 12-lead ECGs. Holter recordings will be downloaded and stored for future analyses. Analyses may be performed for safety assessment or PK/PD modelling as deemed necessary (10 seconds 12-lead ECG extracted to replace potential unevaluable ECG timepoints).

6.6.4.3.2 12-lead ECG assessment

12-lead standard ECGs according to Einthoven, Goldberger and Wilson will be recorded each time after 10 minutes rest in a supine position.

At each time point, the ECG will be recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates will be performed at approximately 1-minute intervals. Each ECG recording (trace) will last 10 seconds. Repeat ECGs will be performed until at least three 10-second ECG records per scheduled time-point meet the quality criteria set out in the Study Operations Manual and the applicable Standard Operating Procedures.

12-lead ECGs will be recorded (25 mm/sec) on 8 to 10-second strips. Heart rate, PR-, QT- and QTc-intervals (Fridericia correction) and QRS duration are measured electronically (with correction by the Investigator, if considered necessary).

All recorded ECGs will be reviewed by a Research Physician and the review will be documented in the source workbook. If a subject shows an abnormal ECG, additional safety recordings (including the use of 12-lead Holter equipment) may be made and the abnormality be followed to resolution if required.

12-lead ECGs will be recorded at the timepoints specified in Timing of repeat measure samples.

12-lead ECG-, vital sign assessment and blood withdrawals should always occur after the nominal timepoints for ECG.

To avoid the need for interpolations in the PK/PD modeling on Day 6 and Day 16, it is important that the time between the end of the triplicate ECG and the respective PK blood draw is within the within the specified time window (see Section 6.6).

Blinding of the ECGs with respect to subject number, treatment period, trial day and time will be performed before ECG analysis by the central ECG laboratory. All ECGs from one subject should be read by the same person at the central ECG laboratory.

QRS and QT intervals as well as heart rate (RR interval) will be measured in superimposed lead on at least 5 QRS complexes.

6.6.4.4 Vital signs

Vital signs (systolic blood pressure [SBP), diastolic blood pressure [DBP], and pulse rate) will be measured by an oscillometric method, each time after at least 5 minutes rest in a supine position.

Vital signs will be recorded at:

- Screening (between Day -21 and -3),
- Day -2 (Admission),
- Day 1 pre-dose,
- Days 6, 16, and 20, and
- EoT

Body temperature

Body temperature will be measured with a calibrated device at:

- Screening (between Day -21 and -3),
- Day -2 (Admission), and
- EoT.

6.6.4.5 Physical examination

The Investigator or his designee will perform a complete physical examination including assessment of at least the skin, eyes, ears, nose, neck, lymph nodes, throat and extremities, plus the following body systems: musculoskeletal, cardiovascular, respiratory, gastrointestinal and neurological. Any other clinically relevant findings will also be recorded.

The physical examination will be performed at:

- Screening (between Day -21 and -3),
- Day -2 (Admission), and
- EoT.

Height and weight will also be measured at:

- Screening (between Day -21 and -3), and
- Day -2 (Admission).

6.6.5 Appropriateness of measurements

For the assessment of safety parameters, standard methods will be used.

Pharmacokinetic measurements will be made using validated methods and parameters derived are appropriate for the trial objectives.

6.7 Data handling

6.7.1 Records and reports

The Investigator ensures the accuracy and legibility of the data reported to AiCuris in the source workbook and electronic Case Report Forms (eCRFs) and in all required reports.

The Investigator should maintain the trial documents as required by the applicable regulatory requirements. The Investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained until at least 25 years after the last approval of a marketing application in an ICH region and until there will be no pending or contemplated marketing applications in an ICH region or at least 25 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however, if required by the local law. It is the responsibility of AiCuris to inform the Investigator when these documents are no longer to be retained.

Upon request of the monitor, auditor, or Regulatory Authority (RA), the Investigator should make all requested trial-related records available for direct access.

Signature authorization form

Before commencement of the trial the Investigator must complete a signature page defining the trial personnel taking part in clinical activities. The Investigator and each employee should be listed on this form with signature, initials (forename and surname), short-form signature and date to identify comprehensibility all data entries, especially corrections performed in the source workbook.

Screening and enrollment log

The Screening and enrollment log sheet must be filed for all subjects participating in the trial who have given their informed consent. Additionally, the date of entry into the trial and the completion date have to be documented in the eCRF.

Source data

Source data are the original records of all variables collected for the trial. They include:

- Signed informed consent
- Individual subject clinical notes
- Records of any procedure performed in accordance with the protocol
- Appropriate sections of the source workbook, where data will be recorded directly into specific forms (eg, PK blood samplings, dosing time, visit dates)
- Trial-specific source documents (eg, ECG print-outs, laboratory print-outs, vital signs, AEs, medical history data)

For all other data generated by calculation or via print-out of equipment, these print-outs are considered as source data and will be filed in the Investigator Folder.

Source Workbook

The Investigator is responsible that all investigations and findings are documented correctly and completely on the source workbook and that all entries are up to date to enable a timely evaluation and validation to identify mistakes at an early stage and to avoid misunderstandings. The correctness of the data should be documented by signing and dating on the respective source workbook. Additional data may also be documented. They should be clearly defined as additional findings and should be justified by the Investigator.

The Investigator agrees to provide direct access to source data/documents for trial-related monitoring, audits, EC review or inspection.

6.7.2 Monitoring

AMS Advanced Medical Services Ltd. Will be responsible for trial monitoring according to ICH-GCP on the Sponsor's behalf. The trial site will be visited at regular intervals by a blinded Trial Monitor to ensure compliance with the trial protocol, GCP and legal aspects. This will include on-site checking of the eCRF for completeness and clarity, cross-checking with source documents (source data review and verification), drug accountability, ISF review, and clarification of administrative matters.

An unblinded Trial Monitor will visit the site pharmacy at the trial start and trial end to ensure correctness of study medication allocation to each patient.

If the on-site monitoring visit is not possible eg, due to COVID-19 limitations, the Trial Monitor will perform a remote monitoring visit as per the applicable AMS Advanced Medical Services Ltd. Procedures and regulatory guidelines.

The Investigators must agree to the inspection of trial-related records by the responsible Regulatory Authority (RA) or by AiCuris. They must allow direct access to source documents to representatives of RA or Sponsor representatives.

6.8 Changes in the conduct of the trial

Any change of the design or procedures of the clinical trial must be described and filed as a administrative letter or in an amendment to this protocol. Any possible implications of the change(s) for the interpretation of the trial must be justified briefly. The time(s) and reason(s) for the change(s), the procedure used to decide on the change(s), the person(s) or group(s) responsible for the change and the nature and content of the data available (and to whom they were available) when the change was made should also be described.

7 DATA MANAGEMENT

The data management department of Richmond Pharmacology will perform data management. The Data Handling Protocol (DHP) will outline the data management process in detail.

The Richmond Pharmacology data management department will:

- develop and maintain the DHP
- set and validate the clinical trial database (Medidata Rave)
- program validation checks
- enter data into the clinical trial database

- review data for accuracy, completeness, and consistency between the CRF and the database
- verify adherence to the clinical pharmacology trial protocol and the DHP.

Screening failure data will not be collected in the EDC.

The database entries will be verified against source data (subject's medical file) by the Trial Monitor during the monitoring visits. The source data verification rate will be 100%.

Clinical data queries will be generated and resolved according to the DHP. Richmond Pharmacology clinical staff, trial RP/PI will assist to resolve clinical data queries.

After all clinical data queries are resolved, final error rate is confirmed, and QC checks are acceptable, the database will be locked. The Investigator will certify that the data entered into the EDC are complete and accurate.

Standard Statistical Analysis System (SAS®) datasets will be generated from the final trial database ready for analyses.

Richmond Pharmacology will perform medical coding. AEs, diagnoses from medical history, and procedures from surgical history will be classified according to MedDRA. Concomitant medication will be coded using WHO-DRUG.

SAEs in the clinical database will be reconciled with the safety database.

Final raw SAS® datasets will be transferred to the statistician and the Sponsor (as applicable).

8 STATISTICS

8.1 Determination of sample size

Simulations by Huang *et al* suggest that using concentration-response analysis, assay sensitivity can be shown with at least 24 subjects [5]. Since in this trial, the time between the 2 periods of the nested crossover is 14 days, it seems prudent to allow for a slightly higher variability of ΔQTc and, therefore, a sample size of 32 subjects has been planned. Assuming a true effect of at most 3 ms, ie, a margin of 7 ms, the power to show absence of an effect of pritelivir is higher than that to show assay sensitivity where the margin may be assumed to be 5 ms. Therefore, 32 subjects in the active group were chosen.

8.2 Definition of trial populations

8.2.1 Safety Set

The Safety Set (SS) will comprise all subjects who receive at least 1 dose of trial medication.

8.2.2 Pharmacokinetics Set

The Pharmacokinetic Set (PKS) will include all subjects in SS who had at least 1 valid plasma concentration-time point to be included in the PK analysis. The PKS will be used for the PK analyses.

8.2.3 ECG Set

The ECG set will include all subjects in the SS who have a valid Baseline and at least one valid post-Baseline ECG. ECGs are considered valid if they are based on at least 2 replicates.

8.2.4 Analysis set for concentration-QT analysis

This analysis set includes the subjects which have a valid baseline and at least one valid post-baseline ECG with for which PK samples were taken and where both the ECG and PK samples were taken within the respective windows. Only those pairs of ECG and PK data where samples were taken within these time windows will be included in this analysis set. Note that a dose reduction is not a reason to exclude a subject from this analysis set.

8.3 Endpoints

ECG variables

The following ECG parameters will be analyzed:

Primary variable (related to the primary endpoint)

- QTc using Fridericia correction method (QTcF)

Secondary variables

- Heart rate
- PR interval
- QRS interval
- Uncorrected QT interval
- Change in ECG morphological patterns

Safety and tolerability

- Overall tolerability
- Nature, frequency, duration, intensity, seriousness, and causality of adverse events
- Physical examination, vital signs, and body temperature
- Clinical laboratory parameters: serum chemistry, hematology and coagulation parameters, urinalysis
- Standard 12-lead ECG

Pharmacokinetics

The following parameters of pritelivir and its metabolites AIC090015 and AIC090105 will be determined:

- C_{0h} (trough levels) of pritelivir, AIC090015 and AIC090105 on the Days 1 to 5 and 13 to 15,
- AUC_{τ}, C_{max}, t_{max}, t_{lag}, CL/F, V_d/F, MRT of pritelivir in plasma on Day 1,
- $AUC_{\tau,ss}$, $C_{ss,max}$, C_{min}, $C_{ss,av}$, t_{max}, CL_{ss}/F, $V_{d,ss}$/F, MRT of pritelivir in plasma on Days 6 and 16,
- AUC_{τ}, C_{max}, t_{max}, t_{lag}, MRT of metabolites AIC090015 and AIC090105 in plasma on Day 1.
- $AUC_{\tau,ss}$, $C_{max,ss}$, C_{min}, $C_{ss,av}$, t_{max}, MRT of metabolites AIC090015 and AIC090105 in plasma on Days 6 and 16.

Moxifloxacin plasma concentrations will be determined for the purpose of the concentration-effect analysis to demonstrate assay sensitivity. The concentrations will be reported, but no pharmacokinetic parameters will be determined.

Pharmacogenomics/ gene expression

Post-hoc analysis of alleles associated with altered drug metabolism/ disposition may be determined.

8.4 Analyses

Details of the statistical analysis will be defined in a Statistical Analysis Plan (SAP). Should there be a need to adapt the trial design following the adaptive features (see Appendix 4), the analysis plan may need to be updated while the principles of the analysis as specified below are maintained. These adaptations will be reflected in the SAP.

8.4.1 ECG variables

Statistical analyses of ECG variables will be performed according to the recommendations provided by the guideline ICH-E14 and its Q&A documents. QTc and HR data will be analyzed using a concentration-effect model. All quantitative ECG parameters will be analysed with respect to their time course using a mixed effects linear model.

In addition, ECG data will be presented as analyses of central tendency (mean, median, standard deviation, minimum and maximum) and categorical evaluations.

Baseline for quantitative ECG variables will be the average of the 3 pre-dose values measured on Day 1.

The primary endpoint is defined as the model based QTcF differences from baseline (ΔQTcF), where baseline is the average of the 3 pre-dose measurements of Day 1. ECGs from Day 1, Day 6 and Day 16 will be used for comparison against baseline. More specifically, a series of linear mixed effect models relating the change from baseline to the concentrations of pritelivir and the metabolites AIC090015 and AIC090105, together or separately, will be fitted. Apart from these concentrations, the models will include fixed effects for time and treatment (Active or placebo) and baseline as a covariate. Random effects per subject for the intercept and, if feasible, for the concentrations included in the respective models will be given. Selection of the primary model will be based on model fit and the Akaike Information Criterion. Predictions of the effect of pritelivir and metabolites at the concentrations seen at t_{max} of each of the moieties involved will be used to exclude an effect of regulatory concern (ie, a one-sided 95 % confidence interval for ΔQTcF completely below 10 ms).

The groups 2a and 2b will be pooled for analysis.

A comparison between moxifloxacin and matching placebo will be done in groups 2a and 2b to demonstrate assay sensitivity using a similar model to the ones described above. Assay sensitivity will be concluded if the lower limit of the one-sided 95% CI for the predicted effect will be >5 ms.

If there are indications that pritelivir has an effect on HR exceeding 10 bpm, HR will also be submitted to a similar analysis. If this confirms an effect exceeding 10 bpm, then an individual

correction will be determined based on the ECG data from Day -1, and QT values corrected according to this method (QTcI) will replace QTcF in the primary analyses.

The appropriateness of the models used will be investigated. In particular, this includes the absence of a delayed effect (respective to all 3 moieties) and any relevant deviations from linearity.

All quantitative ECG variables and their change from baseline will be summarized by timepoint and treatment group. The difference between the 2 treatment groups will also be presented.

Morphological abnormalities will be described and the data will be presented in terms of the number and percentages of subjects under each treatment having changes from baseline that represent the appearance or worsening of the morphological abnormality.

The frequency of outlying values, ie, values satisfying the criteria below, will be tabulated by timepoint and treatment and across all timepoints by treatment:

- Absolute QTcF values >450 ms, >480 ms, and >500 ms
- Change from baseline in QTcF value (ΔQTcF) of >30 ms and >60 ms;
- Fulfilling both, absolute QTcF values >500 ms and ΔQTcF >60 ms;
- Absolute PR values >200 ms, >220 ms, with a pre-dose value below the respective threshold
- ΔPR ≥25%, ie, post-dose PR outside the range of (0.75, 1.25) of the baseline value
- Absolute QRS duration >110 ms and >120 ms
- ΔQRS ≥25%, ie, post-dose QRS outside the range of (0.75, 1.25) of the baseline value
- Absolute HR of <50 bpm or ≥100 bpm
- Heart rate decrease ≥25% from baseline to a HR of <50 bpm and/or increase ≥25% from baseline to a HR of ≥100 bpm.

8.4.2 Pharmacokinetic analyses

Pritelivir and the metabolites AIC090015 and AIC090105

All measured PK variables and derived PK parameters will be listed and summarized by descriptive statistics. Descriptive statistics will be calculated for plasma concentrations of pritelivir and the metabolites AIC090015 and AIC090105 in Group 1 only. Statistics will include sample size (n), mean, standard deviation, coefficient of variation (% CV), geometric mean, median, minimum, and maximum. Dose proportionality of pritelivir will be assessed graphically, by comparing individual dose normalized $C_{ss,max}$, $AUC_{\tau,ss}$, and C_{min} values between the therapeutic and supra-therapeutic dose levels. In Group 2 (moxifloxacin/placebo), pharmacokinetic samples will be drawn to maintain blinding, but will not be analyzed.

Moxifloxacin

Moxifloxacin plasma concentrations will be determined for the purpose of the concentration-effect analysis to demonstrate assay sensitivity. The concentrations will be reported, but no pharmacokinetic parameters will be determined.

8.4.3 Safety analyses

Individual participant demographics (age, gender and race) and body measurement data (height, weight, and BMI) at screening will be listed. These demographic characteristics and body measurements will be summarized by treatment group and overall, using the safety analysis set. Other baseline characteristics will be listed only.

AE data will be listed and summarised using descriptive statistics: the number (and percentage) of participants who experienced any AEs and the number of AE episodes will be summarized for each treatment group. All AEs will be summarized and listed by using the System Organ Class (SOC) and Preferred Term (PT) assigned to the event using the MedDRA. Furthermore, these events will be summarized by their maximum intensity. The number of participants who experienced drug-related AEs will also be summarized. Any SAEs and/or AEs that led to trial withdrawal will be summarized and listed.

Vital signs data (SBP, DBP, pulse rate, temperature) will be listed and summarized, along with changes from baseline, using descriptive statistics (mean, median, standard deviation, minimum, maximum). Out-of-reference-range values will be flagged as high or low and as being clinically relevant or not. The number of participants presenting out-of-range and clinically relevant values will be summarized.

All safety clinical laboratory data will be listed. Laboratory test results will also be compared to laboratory reference ranges. Those values outside of the applicable range will be flagged as high or low, and as clinically relevant or not. The number of participants that present out-of-range, and clinically relevant values, will be summarized. The quantitative laboratory data and changes from baseline will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum). Change from baseline values at each assessment will be calculated as the assessment value minus the baseline value. The qualitative urinalysis data will be listed only.

ECG analyses will be performed on two sets of ECGs: all ECGs prior to adjudication and selected triplicates from each time-point after adjudication (see Section 8.4.1).

All un-adjudicated ECG data (PR, QRS, QT, QTcB, QTcF and HR) and overall ECG evaluation will be listed. ECG data and changes from baseline will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum).

9 ADMINISTRATIVE PROCEDURES

9.1 Ethics Committee and Regulatory Agency approval

It is the responsibility of the PI to submit this CTP, the informed consent document (approved by AiCuris), relevant supporting information, and all types of participant recruitment information to the EC and RA for combined review, and all must be approved prior to the start of participant screening. In addition, advertisements must be approved by the EC and RA prior to use at the site. Prior to implementing changes in the trial, AiCuris and the EC and RA must also approve any substantial amendments to the CTP and corresponding updates to informed consent documents. For non-substantial protocol amendments (that do not require EC regulatory approval) and subsequent updates of the ICF all changes will be done in agreement with AiCuris and Richmond Pharmacology.

9.2 GCP compliance

AiCuris and any third party to whom aspects of the trial management or monitoring have been delegated will undertake their roles for this trial in compliance with all applicable regulations and ICH GCP Guidelines.

Visits to Investigator sites will be conducted by representatives of AiCuris to inspect trial data, participants' medical records, and CRFs in accordance with current ICH Good Clinical Practice Guideline E6 (R2) (2016) and the respective local and national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by competent authorities.

The Investigator must undertake to perform the trial in accordance with ICH GCP Guidelines, EU Directive 2001/20/EC, and the applicable regulatory requirements.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the trial site prior to commitment to participate in this trial. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

The Investigator will maintain a record of appropriately qualified persons to whom the Investigator has delegated significant trial-related tasks. An up-to-date copy of the curriculum vitae for the Investigator, sub-Investigator(s), and essential trial staff will be provided to AiCuris (or designee) before starting the trial.

Agreement with the final Clinical Trial Report will be documented by the dated signature of the PI, in compliance with Directive 75/318/EEC, Directive 2001/83/EC, and ICH E3.

9.3 Regulatory approval

AiCuris (or delegate) will ensure that Local Competent Authority requirements are met before the start of the trial.

9.4 Ethical conduct of the trial

The clinical trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in accordance with the principles of GCP as well as related local legislation.

Possible risks of the planned clinical trial seem to be justifiable from a medical point of view with regard to a possible safer and more effective treatment of future patients.

9.5 Subject information and informed consent

The Investigator (or designee) will inform all subjects verbally and in writing about the nature, significance and scope of the clinical trial. Written informed consent will be obtained from each subject prior to Screening activities. A sample Informed Consent Form will be provided in the Investigator's trial file as a separate document.

All consent documentation must be in accordance with applicable regulations and the ICH Good Clinical Practice Guideline E6 (R2) (2016). Each participant is requested to sign the ICF after they have received and read the written participant information and received an explanation of

what the trial involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the participant's rights and responsibilities.

It must be made completely and unambiguously clear to each subject that he is free to refuse to participate in the trial or can withdraw consent at any time and for any reason, without enduring any penalty or withholding of treatment on the part of the Investigator.

The original signed Informed Consent Form must be kept in the center's file by the Investigator and documented in the eCRF and the subject's medical records. Signed ICFs must remain on file and must be available for verification by Trial Monitors at any time. Another signed original of the ICF must be given to the participant or the participant's legally authorized representative. The PI or delegate will provide the Sponsor with a copy of the EC approved consent forms, and a copy of the EC written approval, prior to the start of the trial.

9.6 Premature termination or discontinuation of the trial

The clinical part of the trial is concluded after the last visit of the last subject has been performed. The Sponsor has the right to close this trial and the Principal Investigator is authorized to set the trial at any point of time on hold, although this should occur only after consulting involved parties. The EC and RA must be informed about this. If the trial/center will be closed prematurely, all trial information, except those that have to remain at the trial center, must be returned to the Sponsor. Destruction of documents/trial medication will be done on notification of the Sponsor.

The trial/center will be terminated prematurely if:

- New toxicological or pharmacological findings or SAEs invalidate the earlier positive benefit-risk-assessment.
- Adverse events occur in such prominence (ie, intensity and frequency) that a continuation of the trial is no longer justified.
- The Sponsor decides to discontinue the clinical trial.

The Investigator must inform his/her local EC about the termination of the trial at this site and the particular reasons for it. He/she should also inform subjects currently included.

9.7 Confidentiality

For the purposes of this Section, "Applicable Data Protection Law" shall mean (a) the Data Protection Act 2018; (b), the UK GDPR (as defined in Section 3(10) of the Data Protection Act 2018) and (c) the General Data Protection Regulation ((EU) 2016/679) as applicable, and any applicable legislation introduced in the UK.

Data collected during this trial may be used to support the development, registration, or marketing of medicinal product. AiCuris will control all data collected during the trial and will abide by the Applicable Data Protection Law. For the purpose of the Applicable Data Protection Law, AiCuris will be the data controller. To the extent that Richmond Pharmacology processes personal data on behalf of AiCuris, in relation to such data Richmond Pharmacology shall only act in accordance with the terms of this protocol and AiCuris's reasonable written instructions and Richmond Pharmacology shall take appropriate technical and organisational measures against the unauthorised or unlawful processing of such personal data.

After participants have consented to take part in the trial, their medical records and the data collected during the trial will be reviewed by AiCuris and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of AiCuris; national or local regulatory authorities, and the EC which gave its approval for this trial to proceed.

Although participants will be known by a unique number, their date of birth will also be collected by Richmond Pharmacology and used to assist AiCuris to verify the accuracy of the data, for example, that the results of trial assessments are assigned to the correct participant. The results of this trial containing the unique number, date of birth, and relevant medical information including ethnicity may be recorded and transferred to and used in other countries throughout the world. If personal data is transferred outside the UK, Richmond Pharmacology will ensure applicable data transfer mechanisms are in place to ensure the data receives essentially equivalent protection as are applicable in the UK. The purpose of any such transfer would be to support regulatory submissions made by AiCuris in such countries. The Parties agree to comply with the relevant provisions of the Applicable Data Protection Law and any directions issued by the UK Information Commissioner's Office in its processing of such personal Data. All nominative information in the participant's medical record will be kept strictly confidential. Nominative information shall mean the name, the address and all other personally identifiable information associated with a participant's name. AiCuris access to participant's data shall be performed in such a way that no participant could be identified by such data.

If there are any contradictions in terms of confidentiality requirements, the requirements of Applicable Data Protection Law will prevail.

To the extent that Richmond Pharmacology processes personal data on behalf of AiCuris, the terms of Appendix 6 shall also apply.

10 ADMINISTRATIVE RESPONSIBILITIES

10.1 Protocol adherence and Investigator agreement

The PI and delegates must adhere to the CTP as detailed in this document. The PI will be responsible for including only those participants who have met CTP eligibility criteria. The PI will be required to sign an Investigator Agreement to confirm acceptance and willingness for themselves and delegates to comply with the CTP.

10.2 Ethics

It is the Investigator's responsibility:

- To ensure compliance with the principles of the current version of the Declaration of Helsinki, GCP standards and local laws and regulations concerning clinical trials.
- To obtain a positive vote for the trial from the appropriate independent EC before the trial starts.
- To inform at least once a year the EC on the clinical trial status.
- To obtain and document informed consent from each subject participating in the trial, before any trial-specific procedure is performed. The consent must be obtained after the explanation of the aims, methods, benefits, and potential risks of the trial.

10.3 Indemnity/liability and insurance

AiCuris will adhere to the recommendations of the Association of British Pharmaceutical Industry (ABPI) Guidelines. A copy of the Indemnity document will be supplied to the Investigator before trial initiation.

AiCuris will ensure that suitable insurance cover is in place prior to the start of the trial. An insurance certificate and a statement of insurance will be supplied to Richmond Pharmacology.

10.4 Protocol management

All protocols and amendments will be prepared by AiCuris. If it becomes necessary to issue a protocol amendment during the trial, AiCuris will notify the Investigator and collect documented Investigator Agreement to the amendment.

10.5 End of trial notification

Richmond Pharmacology on behalf of AiCuris will submit an end of trial notification to the competent authority of the Member State within 90 days of the end of the trial in accordance with EU Directive 2001/20/EC as found on the legislation.gov.uk website. The PI will be responsible for submitting these to the EC and RA through combined review within 90 days of the end of the trial.

For the purposes of this notification, the end of the trial will be defined as database lock.

10.6 Documentation and retention of records

After completion of the trial, all documents and data relating to the trial will be kept in an orderly manner and securely by the PI in a secure file and/or electronically. The data will be available for inspection by AiCuris or their representatives. Essential documents must be retained for 25 years after the final marketing approval in an ICH region or at least 25 years have elapsed since the formal discontinuation of clinical development of pritelivir. The PI or delegate must contact AiCuris before destroying any trial-related documentation and it is the responsibility of AiCuris to inform the investigative site of when these documents can be destroyed. In addition, all participant records and other source documentation will be kept for a longer period if required by the applicable regulatory requirements.

10.7 Monitoring

AMS Advanced Medical Services Ltd. will be responsible for trial monitoring according to ICH-GCP.

10.8 Data management

Richmond Pharmacology will be responsible for data management.

10.9 Statistics

Statistical analysis and reporting will be performed by Richmond Pharmacology for safety and demographics and by Venn Life Sciences for pharmacokinetics.

10.10 Report writing

AiCuris will be responsible for the Clinical Trial Report according to ICH-E3 guideline.

10.11 Posting or submission of summary of clinical trial report to competent authorities of member states concerned and ECs

AiCuris or delegate will post result-related information on this clinical trial to the European Database (which is considered as the submission of a summary of the clinical trial report) within one year of the end of the complete trial to the competent authority of the Member State concerned as required by the regulatory requirement and to comply with the Community guideline on Good Clinical Practice. Richmond Pharmacology on behalf of AiCuris will submit a summary of the clinical trial report to the concerned EC via combined review.

10.12 Quality assurance

The trial results and the corresponding source data/documents must be made available by the Investigator for trial-related monitoring, audits, EC review or inspection by the CA.

10.13 Financing and insurance

Financing of this trial is the responsibility of AiCuris and is detailed in a separate document.

AiCuris provides a certificate of insurance for trial subjects. During the trial, subjects will be insured as a subject of the trial according to the national regulations.

10.14 Publication of results

By signing the trial protocol, the Investigator agrees that AiCuris reserves the right to publish or not publish the data from this trial. For any publication a manuscript will be prepared by AiCuris and AiCuris reserves the right to select the Investigator(s) who will be authors and undertake review of the manuscript before publication. AiCuris will allow the selected Investigators 45 days for full review of the manuscript before publication.

For the avoidance of doubt, the Investigator must not publish the data from this trial without Sponsor's prior written consent. In the event that AiCuris gives its consent, then the Investigator agrees to provide AiCuris with the planned publication in due time, at least 45 days prior to its submission. If AiCuris disagrees with any wordings, interpretations, or conclusions, then AiCuris has the right to request revision(s), meaning that subject to the requirement for scientific objectivity and neutrality AiCuris retains the right to request revision and to have editorial control of such data and trial findings prior to publication.

If any CRO would like to publish or present partial or complete data from this trial, it must obtain prior written permission from AiCuris. In the event of AiCuris giving its consent, CRO agrees to provide AiCuris with the planned publication for its review at least 45 days prior to its submission. Statements on the proposed publication, from AiCuris, must be taken into account prior to publication. The final proposed publication must be formally cleared by AiCuris prior to publication in any journal or other format.

REFERENCES

1. Bloomfield, D.M., et al., *The effect of moxifloxacin on QTc and implications for the design of thorough QT studies.* Clin Pharmacol Ther, 2008. **84**(4): p. 475-80.
2. Culley, C.M., et al., *Moxifloxacin: clinical efficacy and safety.* Am J Health Syst Pharm, 2001. **58**(5): p. 379-88.
3. E14 Implementation Working Group, *ICH Guideline E14/S7B: clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential - questions and answers - Step 5*. 2022: Geneva, Switzerland.
4. Food and Drug Administration, *Guidance for Industry - E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*. 2005: Rockville, MD, USA.
5. Huang, D.P., et al., *Assay sensitivity in "Hybrid thorough QT/QTc (TQT)" study.* J Biopharm Stat, 2019. **29**(2): p. 378-384.

11 SUMMARY OF CHANGES

11.1 Protocol Version 2

The protocol V2.0 was primarily issued to address comments from the MHRA. At the Agency's request, the following changes were made to the protocol:

The selection criteria for the trial population were modified with regard to core laboratory parameters and concomitant medications.

The rules for suspension of dosing in case of adverse reactions were modified for severe adverse reactions, hematological reactions, liver reactions, and dermatological reactions.

In addition, minor typographical corrections were made.

APPENDIX 1 DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS (CORRECTED VERSION 2.1, JULY 2017)

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: <u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage

Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies

In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*) ≥ *7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 ≥ *3.38*
< *7 days of age*	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 ≥ *1.8*
Calcium, Low (mg/dL; *mmol/L*) ≥ *7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< *7 days of age*	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] **or eGFR, Low** **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], High (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

APPENDIX 2 RULES IN THE EVENT OF A DRUG-RELATED AE

RULES IN THE EVENT OF AN ADVERSE REACTION

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

The following tables show the individual subject rules and the trial progression rules, which will only apply to AEs/SAEs where there is a reasonable possibility of relationship to the IMP (ie, adverse reactions [ARs] and serious adverse reactions [SARs]). Grading of AEs will be performed as described in Section 6.6.4.1.4 of the CTP.

RBC has the option to unblind a participant if deemed necessary. If moxifloxacin or either of the two placebos are found to be the cause of the unblinding event in question, then the trial may proceed without a substantial amendment being submitted to EC/RA.

Respective ARs resulting from safety laboratory abnormalities must be confirmed by a control measurement before an action is taken.

Global action rules in the event of an adverse reaction

Serious adverse reaction

If an SAR in any subject, further dosing of all subjects will be suspended.

Re-commencement of dosing will require regulatory approval via a substantial amendment [a)].

Moderate AR (DAIDS Grade 2)

In the event of moderate ARs, trial medication may be continued as planned, continued at a reduced dose [b)], or discontinued in accordance with Investigator's clinical judgment.

Severe AR (DAIDS Grade 3)

In the event of a severe AR in a single subject, trial medication will be discontinued.

If ≥2 subjects experience severe ARs, further dosing of all subjects will be suspended.

Re-commencement of dosing will require regulatory approval via a substantial amendment [a)].

Potentially life-threatening or fatal AR (DAIDS Grade ≥4)

If a potentially life-threatening or fatal AR in any subject, further dosing of all subjects will be suspended.

Re-commencement of dosing will require regulatory approval via a substantial amendment [a)].

Action rules in the event of a hematological adverse reaction

Investigator's judgement will be used to determine which of the pre-dose measurements are considered the baseline. Where possible, the baseline value should be the one that was taken at the closest time of day to the samples being assessed for change, to account for diurnal variation.

If the hematological ARs described below occurring in a single subject, trial medication will be discontinued.

If ≥2 subjects each have the same hematological ARs described below (ie, both subjects having the same PT), further dosing of all subjects will be suspended. Re-commencement of dosing will require regulatory approval via a substantial amendment [a].

- Hemoglobin drop of >25% from the baseline value (which is above the lower limit of normal) to a value below the laboratory reference range, or to an absolute value of <100 g/L
- Platelet count drop of >25% from the baseline value (which is above the lower limit of normal), to a value below the laboratory reference range, or to an absolute value of <120 x 10^9/L
- Clinically significant neutrophil drop, defined as requiring of additional investigation or treatment to properly manage the finding
- Any other hematological toxicity which in the opinion of the Investigator would preclude further dosing in a participant

a) A substantial amendment may include an amendment to the protocol, the ICF, or other trial related documents as appropriate.

Action rules in the event of a liver adverse reaction

Action rules in the event of liver ARs are described in Table 1.

Table 1 Action rules in the event of liver ARs

Threshold	Action rules for individual subjects	Action rules for trial progression
ALT or AST value >3 x and <5 x ULN	Trial medication may be continued as planned, continued at a reduced dose [b], or discontinued in accordance with Investigator's clinical judgment	If ≥4 subjects: Further dosing of all subjects will be suspended. Re-commencement of dosing will require regulatory approval via a substantial amendment [a].
ALT or AST >3 to <5×ULN, and symptomatic [c], ALT or AST value >5×ULN ± symptoms [c]	Trial medication will be discontinued	If ≥2 subjects: Further dosing of all subjects will be suspended. Re-commencement of dosing will require regulatory approval via a substantial amendment [a].
ALT or AST value >3×ULN and bilirubin >1.5 x ULN, without other evidence of cholestasis	Further dosing of all subjects will be suspended. Re-commencement of dosing will require regulatory approval via a substantial amendment [a].	

ALT=alanine aminotransferase; AR=adverse reaction; AST=aspartate aminotransferase; ULN=upper limit of normal

a) A substantial amendment may include an amendment to the protocol, the ICF, or other trial related documents as appropriate.
b) See Section: Dose reduction schedule, below.
c) Symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN).

Action rules in the event of a dermatological adverse reaction

Action rules in the event of dermatological ARs are described in Table 2.

Table 2 Action rules in the event of dermatological ARs

Threshold	Action rules for individual subjects	Action rules for trial progression
Moderate (DAIDS Grade 2)	Trial medication may be continued as planned, continued at a reduced dose [b], or discontinued in accordance with Investigator's clinical judgment. Close monitoring of AE and dermatology consultation to be sought.	If ≥4 subjects: Further dosing of all subjects will be suspended. Re-commencement of dosing will require regulatory approval via a substantial amendment [a].
Severe (DAIDS Grade 3)	Trial medication will be discontinued. Close monitoring of AE and dermatology consultation to be sought.	If ≥2 subjects: Further dosing of all subjects will be suspended. Re-commencement of dosing will require regulatory approval via a substantial amendment [a].
Potentially life-threatening (DAIDS Grade 4)	Further dosing of all subjects will be suspended. Re-commencement of dosing will require regulatory approval via a substantial amendment [a].	

AE=adverse event; AR=adverse reaction

a) A substantial amendment may include an amendment to the protocol, the ICF, or other trial related documents as appropriate.
b) See Section: Dose reduction schedule, below.

Action rules in the event of a cardiac adverse reaction

If a subject has a sustained prolongation of the uncorrected QT interval ≥500 ms, the subject may be monitored for one additional dosing and if shown to be consistent with a dose response, then

trial drug administration will be reduced in dose or suspended, using consistent, technically valid triplicate ECG.

The following rules will apply:

If QT prolongation first occurs on Day 1

- Participant may continue to D2 100 mg pritelivir or placebo dosing. If QT prolongation is sustained following dosing on D2 then individual participant to stop the trial.
- If QT prolongation is not sustained, then the participant can continue to dose at 100 mg up to D6 and to 400 mg from D7 onwards.
- If QT prolongation recurs on D2-D6: individual participant to stop the trial.
- If QT prolongation recurs on D7-D16: individual participant's dose will be reduced [b)]. If QT prolongation is sustained or recurs at any time following dose reduction, participant to stop the trial.

If initial QT prolongation presents on D2-D6

- Participant may continue and be monitored for one additional dose. If QT prolongation is not sustained, participant can continue; if QT prolongation is sustained, then individual participant to stop the trial.
- If QT prolongation recurs until D6: individual participant to stop the trial.
- If QT prolongation recurs on D7-D16: individual participant's dose will be reduced [b]. If QT prolongation is sustained or recurs at any time following dose reduction, participant to stop the trial.

If initial QT prolongation presents on D7-16

- Participant may continue and be monitored for one additional dose. If QT prolongation is not sustained, participant can continue.
- If QT prolongation recurs on D7-D16: individual participant's dose will be reduced [b)]. If QT prolongation is sustained or recurs at any time following dose reduction, participant to stop the trial.

If ≥2 subjects discontinue due to sustained prolongation of the uncorrected QT ≥500ms

- Further dosing of all subjects will be suspended.
- Re-commencement of dosing will require regulatory approval via a substantial amendment [a)].

a) A substantial amendment may include an amendment to the protocol, the ICF, or other trial related documents as appropriate.
b) See Section: Dose reduction schedule, below.

Dose reduction schedule

Dose reduction is not possible if the adverse reaction occurs during D1 to D6 dosing.

For adverse reactions that occur during the 400 mg/day supratherapeutic dosing period (D7 to D16), the following rules apply regarding reduction to 200 mg/day dosing.

Table 3 Schedule for dose reductions from 400 to 200 mg/day pritelivir

Day of AR	Dose reduction
Day 7	• Dosing will either continue at the 400 mg dose (if above rules permit), or will be discontinued and subject withdrawn from the trial. • Dose reduction is not possible as plasma concentrations (exposure) after the first 400 mg pritelivir dose are at the predicted 200 mg/day concentration in steady state.
Day 8	• No dose Day 9 • 200 mg/day Days 10 to 16
Day 9	• No dose Day 10 • 200 mg/day Days 11 to 16
Day 10	• no dose Days 11 and 12 • 200 mg/day Day 13 to 16
Day 11	• no dose Day 12 and 13 • 200 mg/day. Day 14 to 16
Day 12	• no dose Day 13 and 14 • 200 mg/day Day 15 to 16
Day 13	• no dose Day 14 and 15 • 200 mg/day Day 16
Day 14	• no dose Day 15 and 16
Day 15	• no dose Day 16

AR=adverse reaction

APPENDIX 3 RISK MITIGATION TABLE

Potential risks

Pritelivir

There is previous Phase 1 and Phase 2 clinical experience with Pritelivir. Potential risks will be closely monitored as part of the safety evaluations being performed in this trial. The risk mitigation measures are summarized below:

Table 1 Summary of potential risks and respective risk mitigation

Target System	Effect	Risk Mitigation
Renal and Urological System	No effect on renal function was observed in safety pharmacological studies. Pritelivir is renally excreted but no effect on renal function has been seen so far in any clinical or non-clinical studies.	1) Standard monitoring as with all early phase trials. 2) Safety bloods including urea and creatinine as well as glomerular filtration rate will be taken at regular intervals highlighted in the schedule of assessments. 3) Additional assessments may be completed if more than trace protein is found in the urine (including renal ultrasound, unscheduled microscopy or 24-hour urine collection).
Hepatic System	Non-specific increases in ALT and AST seeing in Phase 1 and 2 trials. These were not directly related to pritelivir.	1) Increased monitoring of subjects. 2) Extensive liver function testing will be completed including ALP, AST, ALT, GGT, total protein as well as albumin and globulin, and coagulation will be measured as per the clinical schedule of assessments. 3) Specific inclusion and exclusion criteria will be used to select potential subjects. 4) Previous exposure to hepatitis B (+/- D) and C will be assessed (excluding subjects who have previous exposure). 5) Specific AR rules will be implemented. 6) Additional assessments could be added depending on clinical requirements, including a fibro scan of the liver. 7) Any subject who may have been previously exposed to a biologic drug, will not be included.

Target System	Effect	Risk Mitigation
		8) Additional investigation of CYP isoforms can be performed if any concerning data emerges from ECG, PK or AE analysis.
Cardiovascular system	No effect noted in nonclinical studies. No effect seen in human Phase 1 and 2 trials	1) Standard monitoring as with all early phase trials 2) Thorough QT trial, so extensive cardiac monitoring will be conducted 3) ECG intensive days and thorough Holter analysis
Respiratory System	No effect noted in nonclinical studies. No effect seen in human Phase 1 and 2 trials.	1) Standard monitoring as with all early phase trials.
Central nervous system	No effect noted in nonclinical trials. Non-specific CNS effects seen. Headache, fatigue, dizziness, insomnia commonly seen in Phase 1 and 2 trials after pritelivir and placebo treatment.	1) Standard monitoring as with all early phase trials
Haematological system	Anaemia in dogs and monkeys after repeated oral dosing. Decreased hematocrit; decreased hemoglobin seen in human Phase 1 and 2 trials (after verum and placebo treatment).	1) Standard monitoring as with all early phase trials 2) Subjects will be excluded from this trial if they suffer with anemia or other hemoglobinopathy 3) Specific Adverse Reaction rules regarding reduction in hemoglobin, platelets and neutrophils
Gastrointestinal system (including taste)	Compound depositions (crystalloid spaces) and associated foreign body reactions were observed histopathologically at high dose levels in mice, rats and monkeys mainly in the digestive tract. Non-specific GI disturbance (nausea, diarrhea, abdominal pain and constipation) commonly seen in Phase 1 and 2 trials after pritelivir and placebo treatment.	1) Standard monitoring as with all early phase trials 2) Any self-reported GI disturbance will be investigated further with appropriate investigation 3) Subjects will be excluded from this trial if they have any previous history of Irritable Bowel Syndrome/Inflammatory Bowel Disease or known conditions that may affect absorption in the GI tract. 4) Subjects will not be dosed with pritelivir and moxifloxacin concomitantly

Target System	Effect	Risk Mitigation
Skin	Rash, pruritus, erythema and dry skin seen in a Phase 1 trial with repeated doses of 400 mg/day. Diffuse hair thinning, discolored areas, crusts on the head, and scabby skin correlating histopathologically with a cytotoxic interface dermatitis and perifollicular inflammation in a chronic monkey toxicity study.	1) Standard monitoring and regular AE checks as with all early phase trials 2) Daily skin examination during in-house period and follow up. 3) Subjects will be excluded if they have any previous history of dermatological conditions 4) If dermatological AE of DAIDS Grade 2 occurs, then dermatology consultation to be sought. If deemed treatment related dose reduction or dose suspension to be considered. 5) If dermatological AE of DAIDS Grade 3 trial medication to be stopped for that participant. See AR rules for further details. 6) Supratherapeutic dose may be reduced when skin effects occur during supratherapeutic dosing phase.
Reproductive system	Non teratogenic in rats and rabbit studies. Reversible treatment related effects on male rat fertility consisting of a decrease in epididymal sperm concentrations and motility and presence of abnormal sperm morphology. No effects were seen even at the highest dose level (1,000 mg/kg/day) in sexually mature monkeys over a treatment period of 39 weeks. Therefore, these findings in rats are considered unlikely to be relevant to humans.	1) Specific contraceptive requirements will be in place for subjects. 2) Contraceptive guidance will be used in inclusion criteria. 3) Female subjects will need evidence of negative pregnancy tests prior to dosing.
Lymphatic System	Mild lymphadenopathy noted in pritelivir treated subjects all of which resolved by follow up.	1) Standard monitoring as with all early phase trials 2) Any self-reported lymphadenopathy will be investigated further with appropriate examination and investigation.

Target System	Effect	Risk Mitigation
Ophthalmology	Lenticular opacities (cataracts) and lenticular swelling seen in nonclinical studies in rats and mice. These findings were not observed in non-rodent species. Considered as highly unlikely to be relevant to humans. No visual disturbance seen in human Phase 1 and 2 trials	1) Standard monitoring as with all early phase trials 2) Any self-reported visual disturbance will be investigated further with thorough examination 3) Subjects will be excluded from this trial if they have any previous history of impaired vision

APPENDIX 4 ADAPTIVE FEATURES OF TRIAL DESIGN

This trial incorporates the use of an adaptive design. Trial specific adaptive features and their limits are described in Table 1 below.

Adaptive features may be implemented only with the approval of the Sponsor. Implementation of adaptive features affecting all following subjects will be documented in a non-substantial amendment.

The exceptions to this are the Generic Adaptive Features, which relate to volunteer safety (see Table 2). These may be implemented at the discretion of the Investigator and recorded in that volunteer's source data.

Table 1 Adaptive protocol features - trial specific

Adaptive Trial Design Areas (trial-specific)	Features	Limits
Dose	Dosing	Higher dose may be down titrated to 200 mg per day for individual subjects (please refer to AR rules table)

AR=adverse reaction

Table 2 Adaptive protocol features - generic

Adaptive Trial Design Areas (generic)	Features	Limits
Samples and Assessments (safety)	1) Additional safety assessments may be performed on an individual subject if it is considered clinically necessary by the PI for individuals on a case-by-case basis. 2) Additional safety assessments (including but not limited to laboratory safety samples, vital signs and ECGs) may be added to the schedule of assessments at additional time points for following subjects if the PI considers it necessary from a safety/tolerability perspective, on the basis of evolving data and dosing regimens. 3) Additional safety assessments may refer to either:	1) For individuals, a maximum number of safety blood samples will be determined on a case-by-case basis and cannot be pre-defined as investigations will be performed as necessary to ensure the safety of the individual subject. 2) Trial specific maximum blood volume will not be exceeded (300 mL, see Section 6.6.3 of the CTP). 3) If additional time points for safety assessments are required for following subjects, this will be documented in a non-substantial amendment, providing the overall risk profile of [IMP] has not changed.

Adaptive Trial Design Areas (generic)	Features	Limits
	a) An increased number of the same safety assessments planned in the existing schedules of assessments. b) Additional parameters (specific tests) on assessments already scheduled, eg, troponin tests on safety blood samples. c) Additional safety tests requiring additional blood/urine sample collections or other clinical procedures (eg, ultrasound scans). 4) The timing of safety assessments including but not limited to laboratory safety samples, vital signs and ECGs may be adjusted in accordance with evolving data and dosing schedule. 5) Specialist referrals (eg, to a cardiologist) may be made (and may include all relevant assessments and investigations) if it is considered clinically necessary by the PI, Sponsor, or RBC for individuals on a case-by-case basis	4) If additional safety assessments or parameters are required for following subjects and have a similar risk profile to those planned in this trial protocol, they will be documented in a non-substantial amendment. Additional safety assessments required for upcoming group that are more invasive or have a different risk profile to those in this current protocol must be detailed in a substantial amendment. 5) Alterations in timing of the safety assessments need to be a reflection of the established safety/tolerability and PK profile up to the decision-making time-point. 6) If there are no clinically significant findings in safety assessments anymore, further follow-up may be discontinued. 7) A maximum number of specialist referrals for individuals will be determined on a case-by-case basis and cannot be pre-defined as investigations will be performed as necessary to ensure the safety of the individual participants.
Samples and Assessments (PK)	1) Additional or less blood PK and/or exploratory assessments may be taken in accordance with evolving data and dosing schedule. This includes those for the analysis of metabolites. 2) The timing of blood PK, and/or any potential exploratory assessments may be adjusted in accordance with evolving data and dosing schedule. This	1) Minimum: sufficient PK samples to establish full protocol specific plasma PK profile. 2) Trial specific maximum blood volume will not be exceeded (300 mL, see Section 6.6.3 of the CTP).

Adaptive Trial Design Areas (generic)	Features	Limits
	includes those for the analysis of metabolites.	

CTP=Clinical Trial Protocol; ECG=electrocardiogram; IMP=Investigational Medicinal Product; PI=Principal Investigator; PK=pharmacokinetics; RBC=Risk Benefit Committee

APPENDIX 5 FDA RESPONSE TO TQT TRIAL DESIGN

U.S. FOOD & DRUG ADMINISTRATION

ELECTRONIC MAIL CORRESPONDENCE:
INFORMATION REQUEST/ADVICE

Date: January 13, 2022

To: Irisha Johnson, RAC, Regulatory Affairs Consultant

Sponsor: AiCuris Anti-infective Cures AG

From: Christine Kim, PharmD, RAC-US, Senior Regulatory Project Manager

IND: 104346

Drug: Pritelivir 100 mg oral tablets

Subject: **Study AIC316-03-I-07**

Reference is made to your submission dated December 8, 2021, wherein you provided a comprehensive synopsis for the TQT trial AIC316-03-I-07 for review. Your submission has been reviewed by the multidisciplinary team, including consultation by the Interdisciplinary Review Team for Cardiac Safety Studies. We have the following comments:

Overall, the proposed study design and analysis plan appear acceptable to characterize the effects of pritelivir on the QTc interval.

We have the following additional comments:

1. The adequacy of the dose selection is still a review issue and will depend on the highest therapeutic dose and whether the selected supratherapeutic dose covers the high clinical exposure scenario (i.e., increases in exposure due to drug interaction or organ impairment) of parent and any relevant metabolites for the therapeutic dose.
2. For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "*Scientific white paper on concentration-QTc modeling"* (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "*Correction to: Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).
3. In addition to primary analysis, we recommend that you conduct the by-time analysis using a linear mixed model and perform categorical analysis for all ECG biomarkers (QTc, ΔQTc, HR, PR, QRS, and T-wave morphology).
4. If your product is likely to increase or decrease the heart rate significantly (e.g., >10 bpm) in the study, you will need to consider the use of alternative methods for assessing changes in the QT interval, such as QTcI (individualized QT correction). To support alternative methods, it is important that drug-free baselines are available from a wide enough span of heart rates to cover on treatment changes in heart rate,

within each individual. One way to achieve this could be to have the subjects undergo postural maneuvers (e.g., unsupported sitting and standing) on drug-free visits. In addition, it is also important to account for QT/RR hysteresis prior to deriving the individual QT/RR relationship to avoid bias when estimating the individual QT/RR relationship. For additional information, please see "Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects" (Garnett, C. et al., Am Heart J 2012;163(3):912-30). In the absence of significant heart rate effects, we recommend the use of QTcF for the primary analysis.

5. When you submit your QT evaluation report, please include a completed version of the most recent "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinaryreview-team-cardiac-safety-studies-formerly-qt-irt).

PLEASE REPLY BY EMAIL to confirm receipt at Christine.Kim@fda.hhs.gov. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-5964).

{See appended electronic signature page}

_____

Christine Kim, PharmD, RAC-US
Senior Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINE KIM
01/13/2022 02:31:22 PM

APPENDIX 6 DATA PROCESSING SCHEDULE TO THE PROTOCOL

1. Where RPL processes personal data on behalf of AiCuris, RPL shall act as a data processor and the AiCuris shall be a data controller. To the extent RPL is the data processor on behalf of AiCuris, RPL shall:

1.1 process the personal data only in accordance with the documented instructions of AiCuris;

1.2 implement appropriate technical and organisational measures to protect the personal data against unauthorised or unlawful processing and against accidental loss, destruction, damage, alteration or disclosure. These measures shall be appropriate to the harm and risk which might result from any unauthorised or unlawful processing, accidental loss, destruction or damage to the personal data and having regard to the nature of the personal data which is to be protected and shall include inter alia as appropriate:

1.2.1 the pseudonymisation and encryption of personal data.

1.2.2 the ability to ensure the on-going confidentiality, integrity, availability and resilience of systems and services processing personal data.

1.2.3 the ability to restore the availability and access to personal data in a timely manner in the event of a physical or technical incident; and

1.2.4 a process for regular testing, assessing and evaluating the effectiveness of technical and organisation measures for ensuring the security of processing.

In order to enable RPL to implement appropriate technical and organisational measures, AiCuris shall provide to RPL any information reasonably required by RPL to enable it to assess the appropriateness of such measures.

1.3 only employ or appoint personnel to process the personal data who have given binding undertakings of confidentiality or are under a statutory obligation of confidentiality;

1.4 remain entitled to appoint third party sub-processors. Where RPL appoints a third-party sub-processor, it shall:

1.4.1 ensure that the third party is subject to, and contractually bound by, at least the same obligations as RPL;

1.4.2 provide to AiCuris copies of any documentation to demonstrate compliance with the obligations under this Section 1.4; and

1.4.3 remain fully liable to AiCuris for all acts and omissions of the third party;

1.5 notify AiCuris without undue delay after becoming aware that it has suffered a data breach;

1.6 at AiCuris's cost, permit AiCuris (subject to reasonable and appropriate confidentiality undertakings), to inspect and audit RPL's data processing activities to enable AiCuris to verify and/or procure that RPL is in full compliance with its obligations under the protocol;

1.7 taking into account the nature of the processing, assist AiCuris by appropriate technical and organisational measures, insofar as this is possible, with the fulfilment of AiCuris's obligation to respond to requests from data participants in connection to this protocol exercising their rights under Applicable Data Protection Law;

1.8 unless applicable law requires otherwise, upon termination of the protocol:

1.8.1 at the option of AiCuris comply or procure the compliance with the following:

(a) return to AiCuris all personal data and any other information provided by AiCuris to RPL; and/or

(b) permanently delete all personal data provided by AiCuris to RPL; and

1.8.2 cease to process the personal data.

Notwithstanding the foregoing, RPL shall be entitled to retain personal data to the extent that it is required to do so pursuant to the law of the United Kingdom;

1.9 where the laws of the country where RPL is established require RPL to transfer the personal data to a third country or an international organisation, inform AiCuris as soon as reasonably possible of that legal requirement unless that law prohibits such communication on important grounds of public interest.

1.10 RPL shall only transfer personal data outside the United Kingdom to country or territory that is subject to a UK or European Commission adequacy decision, where appropriate safeguards are in place, and on the condition that the level of protection offered to the data subject in the third country are essentially equivalent to those offered by the Applicable Data Protection Law.